Published in final edited form as:

J Med Chem. 2017 April 13; 60(7): 2605–2628. doi:10.1021/acs.jmedchem.7b00085.

The “Phenylalkylaminome” with a Focus on Selected Drugs of Abuse*

Richard A. Glennon

Department of Medicinal Chemistry, School of Pharmacy, Virginia Commonwealth University, Richmond, Virginia, 23298 USA

Abstract

The phenylalkylamine, particularly phenylethylamine, moiety is a common structural feature found embedded in many clinically-approved agents. Greater still is its occurrence in drugs of abuse or substances with abuse potential. The simplest phenylethylamine, 2-phenylethylamine itself, is without significant central action when administered systemically at moderate doses, but simple structural modifications profoundly impact its pharmacology and result in a large number of useful pharmacological tools, agents with therapeutic potential, and in drugs of abuse (e.g. hallucinogens, central stimulants, empathogens). *In vivo* drug discrimination techniques and *in vitro* receptor/transporter methods have been applied to understand the actions of these phenylalkylamines and their mechanisms of action. Thus far, depending upon pendant substituents, certain receptors (e.g. serotonin receptors) and monoamine transporters (i.e., serotonin, dopamine, and norepinephrine transporters: SERT, DAT, and NET, respectively) have been implicated as playing major roles in the actions of these agents in a complex and, at times, interwoven manner.

Graphical Abstract

*This manuscript is based on an invited presentation provided by Dr. Glennon, recipient of the joint *Journal of Medicinal Chemistry* and ACS Medicinal Chemistry Division Portoghese Lectureship award, at the annual American Chemical Society meeting in Denver, Colorado, March 2015.

Conflict of Interest

There are no conflicts of interests to be reported, and the author no longer has any ties or obligations to any pharmaceutical company mentioned here.

Keywords

Classical hallucinogens; Central stimulants; Synthetic cathinones; Drug discrimination; Serotonin receptors; SERT; DAT; NET

1. Arylalkylamines

Arylalkylamines ($\text{Ar-C}_n\text{-N}$, where n is any whole number) represent one of the most frequently encountered structural scaffolds found amongst pharmacologically- and physiologically-active, naturally-occurring or synthetic substances. The term *arylalkylamine* is quite general. The aryl (Ar) moiety includes substituted or unsubstituted, fused or unfused, aryl or heteroaryl rings distant from a nitrogen atom (N) by a branched or unbranched, saturated or unsaturated, substituted or unsubstituted alkyl chain of unspecified length (and the chain might be tethered back to the Ar group), and where N is a primary, secondary, tertiary, or quaternary amine that might be cyclic in nature or where the N-substituent is incorporated into the alkyl chain or Ar group to form a heterocycle (e.g. a piperidine or tetrahydroisoquinoline). A multitude of compounds has been investigated. But, to many in medicinal chemistry, the term *arylalkylamine* conjures up something more restrictive (although there is probably no logical reason for this), and typically implies a chain length of two carbon atoms between the (hetero)aryl (Ar) and amine (N) moieties. Within the greater domain of *arylalkylamines* are the *phenylalkylamines* – compounds with some of the same structural attributes mentioned above regarding the “alkyl” and “amine” portions, but where Ar is a phenyl (Ph) or substituted phenyl ring. Here, discussion will be restricted, for the most part, to relatively simple phenylalkylamines that possess the general structure Ph-C-C-N where Ph is an unsubstituted or substituted phenyl ring, and C-C is a simple ethyl or substituted ethyl chain (e.g. *phenylethylamines* and *phenylisopropylamines*).

The intent of this article is to highlight the enormity, ubiquity, and pharmacological diversity of agents referred to as arylalkylamines and, more specifically, phenyl-alkylamines (and even more specifically, phenylethylamines). By analogy to the term *genome*, which consists of the entire known gene set, or *receptorome*, which represents the sum total of genes from which receptors are derived (or, alternatively, the sum total of all known receptors), we coined the term *phenylalkylaminome*.¹ To indicate that this was done in jest, we have also referred to this as the *phenylalkylaminegnome* (Figure 1).¹ The term, as indicated by the latter, more whimsical sobriquet, was not meant to be “*scientific*”, but was merely intended to underscore the enormity of this class of compounds.

The *DrugBank* database is a cheminformatics resource that includes information on “approved” small-molecule marketed drugs.² It includes data on 2,198 unique agents, of which 1,991 are classified as *small molecules*, approved for use somewhere in the world. Of these, >1,000 are U.S. FDA-approved drugs. Using *DrugBank* (Version 5.0.2 updated October 1, 2016), a “substructure search” of agents with a molecular weight between 100 and 500 Da, revealed that >10% of approved agents (i.e. 214) contain a phenylethylamine (i.e., Ph-C-C-N) substructure.

It is fairly obvious that although the Ph-C-C-N motif represents a common structural scaffold, pendant substituents play a decisive role in its action(s). For example, the phenylethylamine (**1**; Figure 2) moiety is found embedded in the potent hallucinogenic agent lysergic acid diethylamide (LSD, **2**) – not an “approved” agent (i.e., a U.S. Schedule I Controlled Substance not found in *DataBank*), the analgesic agent morphine (**3**), the antidepressant venlafaxine (**4**), the atypical antipsychotic agent ziprasidone (**5**), and the appetite suppressant lorcaserin (**6**), just to mention a few. It is also found in the 5-HT_{1A} serotonin receptor agonist 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH DPAT; **7**) (Figure 2) and other widely used research tools. This list easily can be extended to include >200 additional “approved agents”, and grows manifold if regulated or unregulated *drugs of abuse* (i.e., “non-approved” drugs or Scheduled substances, and as yet unscheduled substances found on the clandestine market) are considered. As will be seen below, hundreds of *drugs of abuse* and other pharmacological tools are encompassed by the Ph-C-C-N skeleton; these, unless they have an approved use by happenstance (e.g. morphine), are not included in the *DrugBank* database.

One might wonder why Ph-C-C-N (or, more generally, Ar-C-C-N) is such a common structural feature amongst drugs and pharmacologically-active agents. It might be because this moiety is naturally-occurring and commonly found within protein targets (e.g. the amino acids phenylalanine, tyrosine, tryptophan, histidine) or neurotransmitters (e.g. dopamine, norepinephrine, serotonin) and neurotransmitter precursors that interact with various receptor/transporter and enzyme targets that are composed of these amino acids. However, the Ph-C-C-N (and, more generally, Ar-C-C-N) moiety might likely be a source of pharmacologically-active agents because they mimic (e.g. as substrates, agonists) or interfere with (e.g. as blockers/inhibitors/antagonists) actions at those targets (e.g. receptors, transporters, enzymes) that include Ar-C-C-N or Ph-C-C-N moieties. In any event, the Ph-C-C-N moiety, perhaps initially because of synthetic accessibility, or perhaps because so many derivatives were found early on to be of pharmacological value, has been of interest to medicinal chemists since the late 1800s and remains a current pursuit. As simple as the Ph-C-C-N motif might be, it continues to amaze how many simple Ph-C-C-N derivatives have not been pharmacologically evaluated – or even synthesized!

Our studies began in the early 1970s with the question: ‘*Why is it that certain phenylalkylamines (actually, arylalkylamines, in a broader sense) are central stimulants, some are hallucinogens, and yet others possess different actions, or lack central actions altogether?*’. Evidently, although such agents possess a common arylalkylamine or phenylalkylamine backbone, the actions of these agents must rest upon their specific appurtenances (e.g. see Figure 2). Particularly fascinating was the parent member of this family, phenylethylamine (**1**), an agent with minimal central action when administered systemically, and the central stimulant amphetamine (**8**; Figure 3), the simple α -methyl analog of PEA (**1**), whose orally-active central actions have been known for nearly a century. Here, the introduction of a one-carbon unit modified the pharmacology of PEA (**1**).

It must be emphasized that our work was not conducted in a vacuum and that many investigators were working (and continue to work) in the same area. No attempt was made here to be comprehensive or all-inclusive. Our efforts in this area are highlighted. Some of

what follows has been described by us (and others) in review articles over the years, and some of these reviews are cited here in order to reduce the number of references and to provide more over-arching and detailed reading material. Contributions by others that directly impacted our work will either be cited here or, in certain instances, are prominently cited in the papers and reviews mentioned herein.

2. Phenylethylamine

The simplest phenylethylamine, phenylethylamine (**1**) itself, also known as 2-phenylethylamine, 2-phenylaminoethane, phenethylamine, β -phenylethylamine, or simply PEA. PEA (**1**; Figure 2), was first isolated and identified by the Polish chemist Marcell Nencki in 1876 (as reviewed by Grandy³). More than 140 years later, PEA (**1**) and its analogs remain a continuing and fascinating (and, perhaps, growing) topic of interest for medicinal chemists and, as witnessed by the number of new agents appearing on the illicit market, for clandestine chemists as well.

Not only does PEA (**1**) serve as scaffolding for various agents with therapeutic utility (*vide supra*), it possesses activity in its own right. Although found in many plant and animals species, as well as in humans,⁴⁻⁶ PEA (**1**) was initially thought to be a metabolic by-product with no particular physiological relevance.⁵ However, it is now recognized that at very high doses, “several orders of magnitude above its normal physiological range”,⁶ PEA (**1**) can produce amphetamine-like effects in animals (reviewed⁶).

Our early studies involved the use of a peripheral rat fundus tissue preparation to investigate centrally-acting agents; the preparation was known to possess serotonin (5-hydroxytryptamine, 5-HT) receptors, and was also reported to possess tryptamine receptors. This preparation was selected because several centrally-acting *indolealkylamines* (i.e., *tryptamines*) were already known to act at fundus 5-HT receptors as agonists. Just prior to the discovery of multiple subtypes of brain 5-HT receptors (see below), it was found that [³H]tryptamine labeled a population of rat brain receptors distinct from any 5-HT receptor types then known (see Grandy³ for a review). This provided one of the first opportunities for us to examine the binding of centrally-acting arylalkylamines at brain receptors rather than at peripheral fundus 5-HT receptors. We,⁷ and others,³ showed that certain phenylalkylamines, including PEA (**1**), amphetamine, and 4-chloroamphetamine displayed low μ M affinity for [³H]tryptamine-labeled sites in rat brain frontal cortex homogenates. Other arylalkylamines, including certain tryptamines and conformationally-constrained arylalkylamines such as β -carbolines, possessed even higher affinity.^{3,7} Once brain 5-HT receptors had been identified, we abandoned our work with tryptamine receptors in favor of 5-HT.

3. Trace Amine Receptors

Tryptamine and PEA (**1**) had been referred to for some time as *trace amines*, the term *trace amine* being fully described by Usdin and Sandler⁸ in 1976. Although found in human brain, trace amines were present at levels well below those found for common monoamine neurotransmitters and were thought to play a role as neuromodulators.⁸ Other major

endogenous trace amines included the phenylalkylamines p-tyramine and octopamine.⁸ Over the years, trace amines (or their receptors) have been speculated to play a role in attention-deficit hyperactivity disorder (ADHD), schizophrenia, depression, Parkinson's disease, substance abuse, and several other neuropsychiatric disorders (reviewed^{4,6,9,10}). In 2001, the first trace amine receptors were cloned.^{11,12} These receptors are now realized to represent members of a receptor family that are termed *trace amine-associated receptors* (TAARs), and the first member was called TAAR1 (previously TR1 or TAR1). TAAR1 receptors are G protein-coupled receptors associated with stimulation of cAMP (reviewed^{3,13}). Various agents are known to activate TAAR1 including (followed by EC₅₀ value): p-tyramine (69 nM) > PEA (**1**) (240 nM) > tryptamine (310 nM) > octopamine 1,300 nM).¹² Other activating agents included the phenylalkylamine amphetamine optical isomers *S*(+)amphetamine and *R*(-)amphetamine, *S*(+)4-hydroxyamphetamine, *R*(-)4-hydroxyamphetamine, 3-chloroamphetamine, *S*(+)methamphetamine, *R*(-)methamphetamine, and LSD (**2**).¹² In their study, Bunzow et al.¹² found that the presence of a hydroxyl group at the 4-position of PEA-derived structures enhanced potency by several-fold; for example, 4-hydroxyamphetamine (EC₅₀ = 51 nM) was about six times more potent than amphetamine and the most potent activator then identified. However, many of these agents displayed higher affinity/potency at other receptors or targets.

4. Blood-Brain Barrier

In retrospect, it is likely that [³H]tryptamine was labeling a TAAR. However, many TAAR1 ligands including PEA (**1**), tryptamine, and 4-hydroxyamphetamine, have minimal central activity when administered by typical systemic routes of administration. Why are certain phenyl/arylalkylamines, such as these, centrally inactive, or nearly so, when administered systemically? One reason might be that they are unable to readily cross the blood–brain barrier. The concept of the blood–brain barrier (BBB) was proposed as early as 1900 by Lewandowsky¹⁴ (reviewed¹⁵) but was not fully appreciated for many decades to come. Basically, polar substances or substances of low lipophilicity cannot readily cross the BBB because tightly packed endothelial cells in cerebral blood vessels prevent their penetration (except in cases where active transport mechanisms are available – for example, for neurotransmitter precursors). This means that most polar agents (i.e., those that are not very lipophilic – simple phenols, catechols, carboxylic acids, quaternary amines) typically fail (or display a reduced ability) to gain entry to the brain. Other agents, those possessing unprotected primary amines, such as PEA (**1**) or tryptamine – agents of moderate lipophilicity – if they penetrate the BBB, are rapidly metabolized by enzymes such as monoamine oxidase (MAO). As a consequence, polar agents usually possess minimal, if any, central activity.

5. Structurally-modified Phenylalkylamines: A Research Goal

Certain arylalkylamines might not be centrally-acting because of their inability to penetrate the BBB, whereas the actions of others are dictated by their specific substituents. Case in point: the α -methyl analog of PEA (**1**) (i.e., amphetamine; **8**) is a central stimulant whereas the 3,4,5-trimethoxy analog of PEA (**1**) (i.e., mescaline; **9**; Figure 3) is a weak hallucinogenic agent. It had been pretty much accepted at the time our studies began that

amphetamine likely produces its stimulant actions via the dopamine transporter (a fairly new concept at the time), whereas mescaline had been hypothesized to act via interaction at a number of different receptors, including dopamine and norepinephrine receptors (adrenoceptors) whose natural substrates (i.e., dopamine and norepinephrine) bore a striking structural resemblance to mescaline.

One of our initial research goals was to elucidate the mechanism of action of hallucinogenic agents. In 1968, Hollister¹⁶ defined the term “*psychotomimetic*”, which at the time was essentially synonymous with “*hallucinogenic*”, as: “*agents that, upon administration of a single dose, consistently produce changes in thought, mood, and perception without autonomic disturbance or addiction liability*”. His definition was insightful, but quite broad and included agents already (and, certainly, later) recognized as producing different central actions in human subjects (e.g. LSD (2), phencyclidine, and tetrahydrocannabinol – the major active constituent of marihuana). So, a second major goal of ours was to identify which agents produced a common effect. We utilized a 2-pronged approach. First, we used a behavioral technique (i.e., *drug discrimination*) to sort out which agents produced similar “*stimulus*” effects in animals; then, second, we planned to examine those agents from a mechanistic perspective.

6. The Drug Discrimination Paradigm

Over the years, there have been many attempts to develop animal models of hallucinogenic drug action. None has been particularly successful.¹⁷ This was likely due, in part, to the behavioral heterogeneity of the agents being examined.¹⁷ Furthermore, many “*hallucinogenic*” agents profoundly alter an animal’s behavior; but, this is also true of some non-hallucinogenic agents (e.g. central stimulants, analeptics, sedatives, muscle relaxants, anxiolytics, antipsychotics, antidepressants, anesthetics), and such studies were unlikely to afford useful information on mechanism(s) of action if they unknowingly included examples from these different classes of agents. Described below is a procedure we have found useful for our studies, but it is not an animal model of hallucinogenic drug action; rather, it is a model of *stimulus similarity*.

a. Training and stimulus generalization

The drug discrimination paradigm is a behavioral procedure whereby animals, typically rats, are trained to recognize the “*stimulus*” or “*cueing*” properties of a given dose of a *training drug* versus non-drug using a two-lever operant chamber. Training on drug and non-drug (i.e., typically vehicle) conditions, with (sweetened condensed milk or solid food pellet) reinforcement, continues daily. (There are many variations of this paradigm including the use of other animal species, different apparatus, various training and testing conditions, different routes of administration, various schedules of reinforcement, three-lever procedures, and so on; see Glennon and Young¹⁸ for a comprehensive review of the drug discrimination paradigm). Intermittently, generally once per week, and interspersed with continued daily training, reliably-trained animals are administered lower doses of the training drug under non-reinforcement conditions; the animals engender fewer responses on the drug-

appropriate lever such that a dose-response curve can be generated and an ED₅₀ dose calculated for the training drug (Figure 4).

Subsequently, animals can be intermittently administered doses of a non-training drug (i.e., a *challenge drug*), under non-reinforcement conditions, and essentially asked the question: “does this drug produce, at some dose(s), a stimulus effect similar to that of the training drug?”. That is: “Do you (i.e., the animal) recognize the challenge drug as producing a stimulus similar to the training drug?”. This is referred to as a test of *stimulus generalization*. Where stimulus generalization occurs, a dose-response curve can be constructed and an ED₅₀ dose calculated (Figure 4); this process is diagramed in Figure 5. In this manner, the actions and potency of challenge drugs can be compared with that of the training drug. Again, this is not a model of hallucinogenic activity; it is a model of the *stimulus similarity* of drug action. For example, animals trained to discriminate the benzodiazepine anxiolytic agent diazepam will recognize (i.e., *generalize to* or *substitute for* – the terms being used interchangeably) other benzodiazepine anxiolytic agents, but not opioids, central stimulants, hallucinogens, and so on. It also might be noted that although agents that substitute for one another likely produce a common effect (i.e., some aspects of the stimulus properties or “cues” are shared), they need not produce identical effects. Furthermore, agents that substitute for one another seem to do so because they produce similar mechanism-based, not necessarily pharmacology/behavior-based, stimuli. For example, animals trained to discriminate the benzodiazepine anxiolytic agent diazepam do not recognize the arylpiperazine anxiolytic agent buspirone.¹⁸ Whereas diazepam acts as a positive allosteric modulator of GABA_A receptors, the anxiolytic actions of buspirone involve its (partial) agonist action at 5-HT_{1A} serotonin receptors (see below). Thus, this paradigm, in addition to identifying agents that produce a common stimulus effect, is particularly well-suited to investigate mechanisms of drug action.

b. Stimulus antagonism

Another common application of the drug discrimination procedure involves tests of *stimulus antagonism* (Figure 6). Here, doses of various antagonists are administered in combination with the training dose of the training drug under non-reinforcement conditions. Typically, antagonists are first examined in tests of stimulus generalization, as control, to determine whether they might mimic the actions of a training drug (preferably, they should not), or whether they are disruptive to the animals’ lever-responding behavior (i.e., animals’ response rates are monitored). If a combination of training drug plus antagonist dose(s) results in the animals eventually making a decreased number of responses on the drug-appropriate lever (i.e., an increased number of responses on the non-drug lever until the combination elicits vehicle-appropriate responding), it is concluded that the training-drug stimulus has been effectively antagonized. It should be emphasized that the end-point of such studies is not inhibition of the animals’ lever-responding by administration of the antagonist (as determined by monitoring response rate), but a shift in the animals’ responding from the “*drug lever*” to the “*non-drug* (or vehicle) *lever*”. For example, D₂ dopamine receptor antagonists (e.g. haloperidol) block the stimulus effects of amphetamine and cocaine – agents that act via dopaminergic mechanisms – but not those of opioids, which act via an altogether different mechanism, when given in combination, such that the

animals respond on the vehicle-appropriate (i.e., non-drug) lever. Furthermore, returning to the diazepam/buspirone mechanism-based claim made above, the benzodiazepine antagonist flumazenil blocked the stimulus actions of the anxiolytic agent diazepam, but not those of the anxiolytic buspirone, whereas the 5-HT_{1A} receptor antagonist NAN-190 (an agent developed in our laboratories;¹⁹ see below) blocked the stimulus effects of buspirone, but not those of diazepam.¹⁸ The technique is quite useful and of general applicability. If no known antagonist is available for a given agonist whose mechanism of action is understood, antagonists can be developed. This was the case in our development of NAN-190 as an antagonist of the 5-HT_{1A} receptor agonist 8-OH DPAT (**7**) – an agent that served as a discriminative stimulus in rats but for which no antagonist was available. In contrast, antagonists with known receptor selectivity can be used to shed light on the mechanism of action of an agonist whose mechanism of action is unknown.¹⁸

c. Application

The drug discrimination paradigm now has been employed by numerous investigators to examine many hundreds of pharmacologically-active agents in tests of stimulus generalization and stimulus antagonism.¹⁸ The method is commonly used to, for example, *i*) classify the actions of centrally-acting agents, *ii*) determine potencies of similar-acting agents, *iii*) formulate *in vivo* structure-activity relationships, *iv*) identify novel antagonists, *v*) investigate mechanisms of action, *vi*) examine time-course of action (i.e., time of onset, duration of action), and *vii*) determine whether drug metabolites produce stimulus effects similar to their parent agent.¹⁸

Because LSD (**2**) was an established hallucinogen in humans, some of our first studies employed LSD as training drug. It was quickly realized that LSD produced stimulus effects that were training-dose dependent and that the effects might be mediated by different (or sometimes overlapping) mechanisms.¹⁸ Also examined was the indolealkylamine hallucinogen 5-methoxy-*N,N*-dimethyltryptamine (5-OMe DMT; **10**). Here too, stimulus effects were dose-dependent.²⁰ Eventually, we settled on the phenylalkylamine hallucinogen DOM (**11**) as training drug. Rats were trained to discriminate 1.0 mg/kg (i.p.) of DOM from saline vehicle (i.e., the non-drug condition) and tests of stimulus generalization and stimulus antagonism were conducted.

(+)Amphetamine was already a well-documented training drug (reviewed²¹); hence, we used rats trained to discriminate 1.0 mg/kg (i.p.) of (+)amphetamine from vehicle and conducted tests of stimulus generalization and stimulus antagonism. It might be noted that DOM-trained animals did not recognize (+)amphetamine (i.e., the DOM-stimulus did not generalize to (+)amphetamine), and (+)amphetamine-trained animals did not recognize DOM).¹⁸ The stimulus effects of the two agents were mutually exclusive.

Finally, the stage was set to examine various arylalkylamines and to classify them as being hallucinogens (actually, as being DOM-like) or stimulants (or being amphetamine-like). Furthermore, the drug discrimination paradigm, being centrally-mediated, allowed us to identify (or eliminate) agents that did not readily penetrate the BBB barrier. For example, (+)amphetamine-trained animals did not recognize PEA (**1**) or 4-hydroxyamphetamine, nor did DOM-trained animals recognize tryptamine.¹⁸ Returning to the Hollister¹⁶ definition,

DOM-trained animals failed to recognize centrally-acting agents such as phencyclidine, tetrahydrocannabinol, or certain other agents that were included in his original classification; these agents are now realized to produce altogether different stimulus effects, and animals trained to these agents failed to recognize arylalkylamines such as LSD, amphetamine, mescaline or DOM.¹⁸ As a consequence, we were able to sub-classify certain “hallucinogenic agents” – those that substituted for DOM – and termed them ‘*classical hallucinogens*’.

7. Serotonin Receptor Studies

a. Peripheral 5-HT receptors

At the time our studies began in the 1970s, there was evidence for the existence of two populations of peripheral 5-HT receptors: 5-HT-D and 5-HT-M receptors.²² The action of 5-HT at the former was antagonized by dibenzylamine, and at the latter by morphine. LSD (2) was shown to act at the former, and its actions were blocked by dibenzylamine.²² 5-HT-M receptors were eventually, decades later, found to be synonymous with 5-HT₃ serotonin receptors. A variety of isolated peripheral tissue preparations were being used to investigate serotonin receptors, and one of the most popular of these during the 1960s and 1970s was the rat fundus preparation.

Although rat fundus 5-HT receptors were never expressly identified as being 5-HT-D receptors, they bore the hallmarks of such on the basis of drug action. We examined a number of arylalkylamines (indolealkylamines and phenylalkylamines) at rat fundus 5-HT receptors, and later demonstrated that for 14 such agents there was a significant correlation between their 5-HT receptor affinity and both their human hallucinogenic potency (*note bene*: reliable human hallucinogenic potency data were available only on a relatively limited number of agents at the time) and their stimulus generalization potency in DOM-trained rats (reviewed²³).

b. Central 5-HT receptors

In 1979, using a newly developed rapid filtration technique, Peroutka and Snyder²⁴ identified two populations of brain 5-HT receptors: 5-HT₁ and 5-HT₂ receptors. Finally, there was a possibility of examining hallucinogens at brain 5-HT receptors rather than at peripheral 5-HT receptors or [³H]tryptamine-labeled brain binding sites.

Before leaving the topic of fundus 5-HT receptors, it is worth mentioning that attempts were made to determine whether peripheral rat fundus 5-HT receptors bore any similarity to brain 5-HT₁ or 5-HT₂ receptors. The concept of tryptamine receptors had been around for a number of years and it had been speculated that rat fundus might possess both 5-HT and tryptamine receptors. Cohen and Wittenaur²⁵ examined this in detail and concluded that both 5-HT and tryptamine contracted rat fundus by acting on the same population of 5-HT receptors, but via receptors that were distinct from brain 5-HT₁ or 5-HT₂ receptors. This caused us to seriously question the relationships we had identified between peripheral fundus 5-HT receptor affinity and human hallucinogenic action or central DOM-like stimulus activity.

Then, several interesting events occurred. In speaking with Drs. Norm Mason and Ray Fuller during a visit to Eli Lilly & Company, they agreed to examine several of our compounds at the recently identified rat brain 5-HT₁ and 5-HT₂ receptors; it should be noted that these were the only two populations of brain 5-HT receptors known at the time. Although our results were never published, they provided the first supporting evidence that several examples of classical hallucinogens, including DOM, displayed greater affinity for the latter than the former. As might have been expected, Pharma had no particular practical interest in pursuing investigations of hallucinogenic agents.

Later, working with Dr. Milt Teitler (Albany Medical College), we found a significant correlation between the stimulus generalization potency of various agents in DOM-trained animals and rat-brain homogenate 5-HT₂ receptor affinity (see next section).

Sometime later, two populations of brain 5-HT₂ receptors were identified: 5-HT_{2A} and 5-HT_{2C} receptors. Years later, a team from Eli Lilly led by Dr. David Nelson cloned rat fundus 5-HT receptors and found them quite homologous to 5-HT_{2A} and 5-HT_{2C} receptors; they termed these 5-HT_{2F} ("F" for fundus) receptors.²⁶ These have since been renamed 5-HT_{2B} receptors. Subsequently, in collaboration with Dr. Nelson, we demonstrated a significant correlation ($r > 0.9$) for the binding of 16 phenylalkylamines at rat and human 5-HT_{2B} receptors.²⁷ However, 5-HT_{2B} receptors are not a major population of 5-HT₂ receptors in human brain, and the affinities of the agents examined were significantly correlated ($r > 0.9$) with their 5-HT_{2A} receptor affinities.²⁷

Beginning in the early 1980s, we established a long-term relationship with Dr. Teitler who examined many of our compounds at 5-HT₂ receptors – first, at rat-brain homogenate 5-HT₂ and, then, human-brain homogenate 5-HT₂ receptors and, later, at cloned human 5-HT_{2A} receptors. 5-HT_{2C} (initially termed 5-HT_{1C}) receptor binding data were also obtained. Over the years, many additional 5-HT receptors were identified: 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{1E}, 5-HT_{1F}, 5-HT₃, 5-HT₄, 5-HT₅, 5-HT₆, 5-HT₇.²⁸ Each time a new population of 5-HT receptors was identified, several representative classical hallucinogens were evaluated. Most of these studies were conducted in collaboration with Dr. Teitler, some early 5-HT_{1A}, 5-HT_{1B} (initially at the University of Arizona, Tucson), and subsequent 5-HT_{2B} receptor (Eli Lilly) studies were in collaboration with Dr. Nelson, and certain early 5-HT₃ receptor studies were conducted with Dr. Steve Peroutka (Stanford University) and later with Dr. Teitler. Although our primary focus always was on 5-HT₂ receptors, the latter investigations piqued our interest in other populations of 5-HT receptors which we went on to investigate. Such studies, with a few exceptions, will not be described here.

8. Classical Hallucinogens and the 5-HT₂ Receptor Hypothesis

Arylalkylamines we had termed *classical hallucinogens* included indolealkylamines (e.g. LSD, 5-OMe DMT) and phenylalkylamines (e.g. mescaline, DOM). On the basis of drug discrimination studies, we showed that they produced a common DOM-like stimulus effect in rats. This never implied that they produced an identical effect (in humans or animals); rather, they seemed capable of producing a common stimulus effect in animals (i.e., the '*common component concept*'), with certain agents producing additional effects via other

mechanisms. That is, some of these agents, particularly indolealkylamines, also activated 5-HT_{1A} receptors and/or some other receptor population/subpopulation. Notable amongst these agents was 5-OMe DMT (**10**) which displayed even higher affinity at 5-HT_{1A} than at 5-HT₂ receptors (and, note the earlier comment in Section 6c about 5-OMe DMT producing dose-dependent stimulus effects).^{18,20} Other hallucinogenic agents, especially LSD (**2**), were particularly promiscuous and interacted at a variety of neurotransmitter receptors as agonists, partial agonists, or antagonists.¹⁸ But, these agents had the *common* ability to bind, and *activate*, 5-HT₂ receptors. For example, a dozen classical hallucinogens were compared and shown to stimulate 5-HT_{2A}-mediated phosphatidylinositol hydrolysis involved in second messenger signaling.²⁹ Notable among these were DOM (**11**) and its halogenated counterparts DOB and DOI (**12** and **13**, respectively; see Figure 3 for structures).

After examining the discriminative stimulus and 5-HT₂ binding properties of several dozen arylalkylamines, we found that there was a significant correlation between *i*) 5-HT₂ receptor binding affinity and stimulus generalization potency for substitution (stimulus generalization) in DOM-trained animals, *ii*) 5-HT₂ receptor affinity and human hallucinogenic potency, and *iii*) human hallucinogenic potency and drug discrimination potency using DOM-trained animals (reviewed³⁰). The 5-HT₂ hypothesis of hallucinogenic drug action (for the *classical hallucinogens*) was proposed. Once cloned, human 5-HT_{2A} receptors were examined and the concept was modified to the “5-HT_{2A} hypothesis” of classical hallucinogen drug action.³⁰

Drs. Jose Leysen and Francis Colpaert (the latter conducting drug discrimination studies using LSD-trained animals) at Janssen Pharmaceutica (Beerse, Belgium) developed the first useful 5-HT₂ receptor antagonists: ketanserin and pipenpirone.^{31,32} They kindly provided us, during a visit to their facilities, with samples of each agent, and we later found that both agents were potent antagonists of the DOM stimulus in tests of stimulus antagonism.^{30,33} Results with these two antagonists supported our initial *5-HT₂ hypothesis of hallucinogenic drug action* for classical hallucinogens. Subsequently, newer 5-HT₂ receptor antagonists were developed and provided by other investigators, examined, and found effective in blocking the DOM stimulus.¹⁸

More than a decade later, Vollenweider et al.³⁴ demonstrated that “psilocybin-induced psychosis” (psilocybin being the phosphate ester of 4-hydroxy-*N,N*-dimethyltryptamine – an indolealkylamine classical hallucinogen) could be antagonized by ketanserin and risperidone (a mixed 5-HT₂/D₂ receptor antagonist) but not by haloperidol (a D₂ dopamine receptor antagonist) in human volunteers. More recently, it has been shown that the disrupting effects of psilocybin on sensorimotor gating in human volunteers was blocked by ketanserin,³⁵ as were psilocybin-induced visual hallucinations.³⁶ Hence, human data, finally, became available to support our receptor- and rodent-based *5-HT₂ hypothesis of classical hallucinogen drug action*.

9. Utility of 5-HT₂ Agonists

a. Development of radioligands

For many years, the tritiated version of the 5-HT₂ receptor antagonist ketanserin, [³H]ketanserin, introduced by Janssen Pharmaceutica was employed as a radioligand for labeling 5-HT₂ receptors; it is still used today. As an aside, probably the two synthetic agents to make the greatest impact on early 5-HT receptor research since the discovery of 5-HT itself (in my opinion), were the 5-HT₂ receptor antagonist ketanserin and the 5-HT_{1A} receptor agonist 8-OH DPAT (**7**).

Although not as much a problem with today's use of cloned and expressed receptors, the lack of ketanserin's selectivity for 5-HT₂ receptors over some other receptors, notably histamine receptors and certain adrenoceptors, was a drawback when brain homogenates were being employed as the receptor source. Prior to the advent of [³H]ketanserin, [³H]spiperone was widely used to label 5-HT₂ receptors; but, [³H]spiperone was already known to tag certain dopamine receptors and was later found to label 5-HT_{1A} receptors as well – the latter finding resulting in the identification and subsequent subdivision of 5-HT₁ receptors into 5-HT_{1A} and 5-HT_{1B} receptors. Because DOM (**11**) represented an agent that lacked affinity for most receptors that [³H]ketanserin and [³H]spiperone labelled, we undertook a structure-activity study to identify novel entities that might be used as new agonist radioligands. Ultimately, we synthesized tritiated DOB (**12**) and radioiodinated DOI (**13**). [³H]DOB was a very effective 5-HT₂ receptor radioligand but saw somewhat limited application – perhaps because DOB is a controlled (U.S. Schedule I) substance and investigators were required to be licensed to use it. [¹²⁵I]DOI, with higher specific activity, and DOI not being a controlled substance, has seen wider application and is currently commercially available and fairly widely used in binding studies. 5-HT_{2A} binding data are provided for several representative agents in Table 1.

[¹²⁵I]DOI has been used in autoradiographic studies with rat brain, and [¹²³I]DOI as a single-photon emission computed tomography (SPECT) imaging agent in monkeys.¹⁸ As an aside, we also employed *R*(-)-DOB, the higher affinity optical isomer of DOB, and (±)DOI as training drugs in drug discrimination studies for comparison with binding data being obtained using [³H]DOB and [¹²⁵I]DOI as radioligands, but these novel training drugs offered no apparent advantage over DOM-trained animals.¹⁸

An added bonus of [¹²⁵I]DOI as a 5-HT₂ receptor radioligand is that agonists generally bind with higher affinity (typically 10-fold or greater) at agonist-labeled receptors than at antagonist-labeled receptors. For example, 5-HT bound with 50-fold higher affinity at rat brain 5-HT₂ receptors labeled by [¹²⁵I]DOI (*K_i* = 10.6 nM) versus receptors labeled by [³H]ketanserin (*K_i* = 600 nM), and DOI displayed nearly 30-fold higher affinity. In contrast, the 5-HT₂ receptor antagonist ketanserin bound with nearly comparable affinity at both (*K_i* = 2.4 and 1.2 nM, respectively, for [¹²⁵I]DOI- and [³H]ketanserin-labeled sites).³⁹ For some time, we employed both [³H]ketanserin and [¹²⁵I]DOI in binding studies to obtain early clues as to whether novel agents might be potential 5-HT₂ receptor agonists or antagonists.

b. Development of 5-HT₂ receptor antagonists

A classical QSAR study was conducted to identify physicochemical properties that might underlie the binding of phenylalkylamines at 5-HT₂ receptors. For a series of greater than two dozen compounds (i.e., DOM-related analogs where the only structural change was replacement of the 4-position methyl group with a variety of substituents), it was found that affinity increased as substituent lipophilicity increased.¹⁸ However, some compounds with high 5-HT₂ receptor affinity failed to substitute in DOM-trained rats. For example, within a homologous series where the 4-position substituent ranged from methyl (i.e., DOM) to *n*-octyl (i.e., DOCT), compounds with substituents larger (longer; bulkier?) than *n*-butyl failed to substitute. Being high-affinity 5-HT₂ serotonin receptor ligands, some (e.g. DOCT) were examined as potential antagonists and, indeed, were able to antagonize the DOM-stimulus when administered in combination with DOM.¹⁸

Another informative lead eventually fueled the discovery of other phenylethylamine-based 5-HT₂ receptor antagonists. Neither PEA (**1**) nor amphetamine (Table 2) nor any of its monomethoxy analogs displayed significant affinity for 5-HT₂ receptors. Some dimethoxy analogs (e.g. **20**, Table 2) showed modest binding when unsubstituted at the 4-position, but affinity was substantially enhanced when certain substituents were present (e.g. DOB; Table 2). It might be parenthetically mentioned that these studies led to the development of [³H]DOB and [¹²⁵I]DOI. Interestingly, replacement of the 4-bromo group of DOB (**12**) with a (3-phenyl)propyl group (i.e., **21**) had no effect on affinity – and, in an agent that did not substitute for DOM in stimulus generalization studies; furthermore, in the case of the latter, the 2,5-dimethoxy pattern, optimal for agonist action, was no longer required for high-affinity binding (e.g. **22** and **23**; Table 2). Ultimately, after further SAR studies were conducted, we developed several phenylalkylamines as 5-HT₂ receptor antagonist; for example **24** and **25** (*K*_i = 20 and 13 nM, respectively) (Figure 7) were found to be inhibitors of 5-HT-induced phosphatidylinositol turnover.⁴⁰ Hence, a potent 5-HT₂ serotonin receptor agonist, DOB (**12**), was converted to several novel 5-HT₂ receptor antagonists. Both DOB and **25** can trace their structural ancestry to PEA (**1**), a compound that lacks affinity for 5-HT₂ receptors (Table 2). It is evident that the agonist and antagonist phenylethylamines do not share a common SAR, and the SAR of the latter remain to be fully investigated. However, this supports the earlier contention that pendant substituents have a dramatic influence on the actions of phenylalkylamines.

c. Development of 5-HT₂ receptor agonists with therapeutic potential

Glaucoma is a leading cause of blindness, and this has been related to increased intraocular pressure (IOP). Reduction of IOP is an effective treatment for glaucoma but some patients are refractory to current therapies. A new direction in reducing IOP was desired. Investigators at Alcon Research identified 5-HT_{2A} receptors in ocular tissue and demonstrated that topical administration of *R*(-)-DOI, a potent 5-HT₂ receptor agonist identified by us, produced a significant decrease in IOP in cynomolgus monkeys. In a collaborative effort with Alcon, our research goal was to identify a novel 5-HT₂ serotonin receptor agonist with reduced lipophilicity so that it would not readily penetrate the BBB to produce untoward (i.e., hallucinogenic) side effects. We selected a high-affinity/high-

efficacy 5-HT₂ serotonin receptor agonist (i.e., DOB) and attempted to reduce its lipophilicity.

How might this be accomplished? We already knew from prior studies³⁷ that replacement of the 4-bromo substituent of DOB with a carboxylic acid, or conversion of DOB to an N,N,N-trimethyl quaternary amine (i.e., QDOB)^{27,42} – both being effective strategies to limit BBB permeability^{14,15} – would not work because both of these compounds lacked affinity for the target receptor.^{37,42}

Another strategy was to unmask one of the two methoxy groups of DOB to provide a polar phenolic group – phenolic groups being known to decrease BBB permeability. We had already examined the two *des*-methyl analogs of DOM: 2-*des*-methyl DOM (2-DM-DOM; **26**) and 5-*des*-methyl DOM (5-DM-DOM; **27**) (Figure 8).⁴³ Both compounds displayed affinity at 5-HT_{2A} receptors, their affinities being approximately one-fifth and one-half, respectively, that of DOM. Furthermore, both compounds substituted in *R*(-)-DOM-trained and LSD-trained animals, suggesting agonist action, and stimulus effects were antagonized by pretreatment of the animals with the selective phenylalkylamine-based 5-HT_{2A} receptor antagonist M100907 (MDL-100,907; volinanserin, **28**).⁴³

Stimulus generalization was demonstrated to be time-dependent, with the phenolic compounds having a longer onset of action time (decreased ability of the agents to penetrate the BBB?). Both of these agents were potential candidates for further investigation. However, there was some concern that 2-DM-DOM and 5-DM-DOM might undergo further O-demethylation *in vivo* to a hydroquinone. It had been shown years earlier that DOM can undergo metabolic *bis*-demethylation to a hydroquinone, and that the hydroquinone undergoes oxidation to a *para*-quinone (and/or a cyclic iminoquinone) that reacts irreversibly with various proteins.⁴⁴ As a consequence, this approach was not pursued because of potential risks of neurotoxicity.

Another approach at reducing lipophilicity was to introduce a polar substituent on the alkyl chain. The first agent examined was morpholine **29** (Figure 8).⁴⁵ However, **29** displayed 100-fold lower affinity than *R*(-)-DOB ($K_i = 0.2$ nM) for [¹²⁵I]DOI-labeled 5-HT_{2A} receptors (and – note the radioligand being employed and implications with regard to agonist action). This might have been expected because N-methylation was already known to decrease the 5-HT₂ receptor affinity of DOB.⁴² Next examined were phenylethylamines **30** and **31** – lacking an α -methyl group (to avoid problems of diastereomeric isomers); **30** and **31** showed improved affinity ($K_i = 2.0$ and 2.1 nM, respectively) relative to **29**.⁴⁵ What was learned was that introduction of small polar substituents at the β -position was tolerated by 5-HT₂ receptors; furthermore, one specific optical isomer of **30** and **31** might have been expected to display even higher affinity, but were never prepared. Instead, we prepared optical isomers of β -methoxy and β -hydroxy DOB. All isomers displayed high affinity for 5-HT_{2A} receptors (Table 3). For both the β -methoxy and β -hydroxy analogs, the *R,R*-isomers (i.e., **35** and **39**, respectively) seemed optimal and their affinity approached the affinity of *R*(-)-DOB. With **39** likely being the more polar and less likely to penetrate the BBB than **35**, due to the presence of the hydroxyl group, investigations continued with **39**. Compound **39** retained the efficacy of *R*(-)-DOB in a calcium-mobilization assay, and reduced IOP in cynomolgus monkeys upon

topical application. Furthermore, in tests of stimulus generalization using DOM-trained animals, **39** was 17 times less potent than *R*(-)-DOB.⁴⁵ So, even though **39** was not without central action, it was considered to possess minimal abuse liability considering its method of application (ocular instillation) and the intention of making available only very dilute ocular solutions of the agent. Then, a turn of events.

In concert with our synthetic and behavioral efforts, Alcon developed AL-38022A (**40**) (Figure 8). Compound **40** was a very high-affinity ($K_i = 0.13$ nM) 5-HT_{2A} receptor agonist with efficacy comparable to *R*(-)-DOI.⁴⁶ In stimulus generalization studies, **40** was more potent than *R*(-)-DOI in DOM-trained rats (ED₅₀ = 0.05 mg/kg and 0.2 mg/kg, respectively, for **40** and *R*(-)-DOI) and equipotent in DOM-trained rhesus monkeys (ED₅₀ = 0.04 mg/kg).⁴⁶ As such, **40** rivaled the potency of LSD (**2**). Furthermore, its actions were blocked using the 5-HT_{2A}-selective antagonist M100907 (**28**). Obviously, compound **40** could not be further considered for therapeutic utility – although it might represent a useful *pharmacological tool*. In an attempt to decrease the lipophilicity of **40**, Alcon prepared several additional compounds and optical isomers and examined them; this ultimately led to compound **41** (Figure 8), the 8-hydroxy counterpart of **40**.⁴⁷ Although **41** displayed 3-fold reduced affinity for 5-HT_{2A} receptors relative to **40**, its experimentally-determined distribution coefficient was >10-fold lower. Furthermore, in rats trained to discriminate DOM from vehicle, **41** produced saline-appropriate responding at ten times the dose of **40**, and effectively reduced IOP following topical application in monkey assays.⁴⁷ From these and other studies, it was concluded that **41** had an overall profile favorable for consideration as a clinical candidate for continued evaluation.

10. MDA, MDMA, and PMMA

As described above, we employed DOM and (+)amphetamine as discriminative stimuli in rats in order to classify various arylalkylamines as acting as DOM-like or amphetamine-like substances. Very early on, we found one agent substituted in both groups of trained animals: 1-(3,4-methylenedioxyphenyl)-2-aminopropane (MDA; **42**) (Figure 9), a fairly popular drug of abuse during the 1960s (the “*love drug*”) that has re-surfaced on the clandestine market in recent years. Because it was the first agent to do so, we subsequently examined MDA optical isomers and found that *R*(-)-MDA, but not *S*(+)-MDA, substituted in DOM-trained animals whereas the reverse was true in (+)amphetamine-trained animals. Furthermore, *S*(+)-MDA, but not *R*(-)-MDA, substituted in cocaine-trained animals.¹⁸ This probably represented the first time optical isomers of a given agent had been shown to produce different stimulus effects in drug discrimination studies with each isomer possessing a defined/different abuse potential.¹⁸

To further investigate this unique and very intriguing phenomenon, we trained rats to discriminate racemic MDA from saline vehicle. Typically, training rats to discriminate a centrally-acting agent from vehicle (depending upon the particular agent) requires 60 to 90 days.¹⁸ Training animals to discriminate racemic MDA (**42**) from vehicle took well over one year – much, much longer than the typical training time of any agent we had previously used as a training drug.⁴⁸ We were of the opinion that the animals were being required to recognize a complex stimulus - two different stimuli. This seemed to be borne out by

subsequent stimulus generalization studies. But, eventually, the animals learned the task. Next, tests of stimulus generalization were conducted with a variety of agents, and ($\pm$)MDA-stimulus substitution occurred with classical hallucinogens such as DOM and LSD, as well as with central stimulants such as (+)amphetamine and cocaine⁴⁹ (and it might be noted that amphetamine and cocaine substitute for one another regardless of which is used as training drug).¹⁸ Substitution also occurred to both optical isomers of MDA.^{18,49} Initially, it was thought that MDA-trained animals might supplant the use of DOM- and amphetamine-trained animals to quickly identify phenylalkylamines as being “active” in producing one of these two types of effects. We soon realized that *i*) if substitution occurred, we would still need to examine the agents in DOM- and amphetamine-trained animals for further classification, and *ii*) the MDA-stimulus training period limited the time we could investigate new agents (i.e., training required 50%–60% of a rat’s typical lifespan). Hence, we ventured a different approach.

In a continuation of the above studies, another group of rats was trained to discriminate *R*(-)MDA from *S*(+)MDA from vehicle in a three-lever drug discrimination task.⁵⁰ Once the animals had been trained, and this took some time, administration of classical hallucinogens such as LSD, mescaline, and DOM engendered *R*(-)MDA-appropriate lever-responding, whereas following the administration of central stimulants such as (+)amphetamine and cocaine, the animals responded on the *S*(+)MDA-appropriate lever.¹⁸ Furthermore, the 5-HT₂ receptor antagonist pirenpirone blocked the *R*(-)MDA stimulus, but not the *S*(+)MDA stimulus.⁵⁰ The results indicated that MDA optical isomers were capable of producing different and enantiospecific stimulus effects in animals. And, this conclusion was supported by being able to train the same group of animals to discriminate between the two optical isomers. However, technical difficulties precluded the use of this paradigm on a wide-scale basis. Nevertheless, the three-lever procedure provided “proof of concept” and was the first to show that animals could be trained to discriminate the stimulus effects of optical isomers of a given agent.

In the 1980s, a new phenylalkylamine emerged on the clandestine market: the N-monomethyl homolog of MDA or methylenedioxymethamphetamine (MDMA, ‘Ecstasy’, currently popular under the name of ‘Molly’, and by several other names and acronyms; **43**). It is probably as popular today as it was then – if not more so. The agent has been termed an *empathogen* because it produces a sense of well-being and other pro-social effects.⁵¹ We first examined MDMA (**43**) in the mid-1980s. Based on SAR that we had established by then, it was our assumption that N-methylation would enhance the central stimulant character of MDA and, at the same time, detract from its hallucinogenic character. We found that *R*(-)MDMA displayed only modest affinity for 5-HT₂ receptors ($K_i = 3,310$ nM) whereas the affinity of its *S*(+)-enantiomer was even lower ($K_i = 15,800$ nM).⁵² This was not inconsistent with the concept that MDMA might be an amphetamine-like agent, and with reports that *S*(+)MDMA was more potent than *R*(-)MDMA in humans.

We, and others (notably Dr. David Nichols and colleagues) examined MDMA and its isomers, and various MDMA analogs, in drug discrimination studies using animals trained to a variety of substances (see Nichols and Oberlender⁵³ and Glennon⁵⁴ for early reviews, and Glennon and Young¹⁸ for a broader overview). MDMA did not substitute in “classical”

hallucinogen-trained (i.e., LSD- or DOM-trained animals), but results in (+)amphetamine-trained animals were mixed. We found that both a (+)amphetamine stimulus and an MDA stimulus generalized to MDMA.⁴⁸ Clearly, MDMA, though neither a simple hallucinogen nor a simple central stimulant, seemed to possess some amphetamine-like qualities.

MDMA has been used as a training drug,^{53,54} and MDMA-stimulus generalization occurred to the central stimulant cocaine; however, cocaine-trained animals failed to recognize MDMA or either of its optical isomers.⁵⁵ Others also found that neither MDMA isomer substituted in cocaine-trained animals, whereas yet others showed that *R*(-)-MDMA, but not *S*(+)-MDMA,⁵⁶ substituted (see Bondareva et al.⁵⁵ for extended discussion). In one study, cocaine did not substitute either in *R*(-)-MDMA- or *S*(+)-MDMA-trained rats,⁵⁷ whereas in another study substitution occurred in *R*(-)-MDMA- but not *S*(+)-MDMA-trained animals.⁵⁵ It is generally concluded that the stimulus actions of MDMA are complex and might be (training) dose-related.¹⁸

In studying the SAR of MDMA as a discriminative stimulus, we found that the MDMA-stimulus generalized to PMMA (**45**), a drug of abuse that has been sold on the clandestine market as representing MDMA (although our studies pre-dated those reports). PMMA might be viewed as the simple 4-methoxy analog of methamphetamine (**52**; see later) or, alternatively, as the N-methyl analog of 4-methoxyamphetamine (PMA; **44**). Both methamphetamine and PMA substituted in (+)amphetamine-trained rats.¹⁸ What was puzzling was that PMMA, which combines both functional groups, did not substitute in (+)amphetamine-trained animals but did so in MDMA-trained animals. Furthermore, like (+)amphetamine, MDMA was a potent locomotor stimulant⁵⁸ whereas PMMA failed to increase mouse locomotor activity up to doses of 30 mg/kg (higher doses were not examined). Because MDA and both its optical isomers substituted in MDMA-trained rats,⁵³ it seemed that aryl substituents, rather than the N-methyl group, were dictating the stimulus action of these agents.

Subsequently, we trained rats to discriminate PMMA (1.25 mg/kg; ED₅₀ = 0.4 mg/kg) from saline vehicle. The PMMA-stimulus generalized to *S*(+)-PMMA (ED₅₀ = 0.3 mg/kg) whereas administration of *R*(-)-PMMA resulted only in partial substitution.¹⁸ The PMMA-stimulus failed to generalize to the hallucinogen DOM or the stimulant (+)amphetamine (i.e., both produced vehicle-appropriate responding at the highest doses tested). PMMA seemed unique. However, the PMMA-stimulus generalized to (±)-MDMA and *S*(+)-MDMA (ED₅₀ = 1.32 and 0.48 mg/kg, respectively), but administration of *R*(-)-MDMA resulted only in partial generalization. The PMMA-stimulus also generalized to (±)-MDA, *S*(+)-MDA, and *R*(-)-MDA (ED₅₀ = 0.5 and 0.7, and 1.5 mg/kg, respectively).¹⁸ Despite some similarity between the actions of MDMA and PMMA, there was ever growing evidence that the two agents were acting differently. For example, the MDMA-stimulus, but not the PMMA-stimulus, generalized to cocaine.¹⁸ This suggested that MDMA might possess more of a dopaminergic (i.e., amphetamine-like) stimulus component of action than PMMA.

1-(3,4-Dimethoxyphenyl)-2-aminopropane (3,4-DMA; **46**) (Figure 9) can be viewed as a “ring opened” analog of MDA (**42**), and PMA (**44**) and MMA (**47**) represent compound **46** minus one of the two methoxy groups. Although PMA and MMA substituted in

(+)amphetamine-trained animals, 3,4-DMA curiously failed to do so. But, 3,4-DMA substituted in MDA-trained animals.⁴⁹ The optical isomers of 3,4-DMA substituted both in MDMA- and PMMA-trained animals with relatively little difference in potency (Table 3). Interestingly, although neither isomer of PMA substituted in MDMA-trained animals, *R*(-)-PMA (but not *S*(+)-PMA) substituted for PMMA and was equipotent with the training drug; in contrast, neither isomer of MMA substituted in PMMA-trained animals, but *R*(-)-MMA (but not *S*(+)-MMA) substituted for MDMA (Table 4). This suggested that the 4-position oxygen atom is more important for PMMA-like action whereas the 3-position oxygen atom favors MDMA-like actions. When both methoxy groups are present, such as in 3,4-DMA, the resulting compound displayed both types of actions and was relatively similar in potency.

It was becoming increasingly apparent that MDA, in addition to binding with modest affinity at 5-HT_{2A} receptors ($K_i = 387$ and 197 nM for ($\pm$)MDA and *R*(-)-MDA), respectively),³⁸ must be doing something else. Why else would there be cross-generalization (or lack thereof) between many of these structurally similar agents. Furthermore, (+)amphetamine and PMMA lacked affinity for 5-HT_{2A} receptors. (+)Amphetamine had been shown to act at monoamine transporters as a substrate (i.e., as a releasing agent); hence, MDA, MDMA, and PMMA were examined at serotonin (SERT), dopamine (DAT), and norepinephrine (NET) transporters (Table 5).

The releasing actions of (+)amphetamine (Table 5) and methamphetamine isomers (data not shown)⁶⁰ are primarily at DAT and NET. In the case of methamphetamine, the potency of the *R*(-)-isomer is somewhat lower than its *S*(+)-isomer by about 2-fold and 17-fold, respectively. For MDMA (Table 5), although active at all three transporters, releasing potency follows the rank order SERT > NET > DAT. PMMA is also more of a serotonin releasing agent, SERT > DAT potency. Perhaps these subtle differences, coupled with the direct action of MDA at 5-HT_{2A} receptors, accounts for the stimulus generalization profiles described above. Rothman and Baumann⁶¹ found that increasing the SERT-releasing action of DAT releasing agents attenuates stimulant-related activity (e.g. self-administration, locomotor activity). It has been speculated that the same might be true for their discriminative stimulus effects.¹⁸ It would seem that further studies are needed to sort this out.

Following an examination of >200 arylalkylamines (indolealkylamines and phenylalkylamines) in drug discrimination studies using animals (Sprague-Dawley rats) trained to discriminate the hallucinogen DOM, the central stimulant (+)amphetamine, or the agents MDA, MDMA, and PMMA from saline vehicle, we proposed that their stimulus actions might be classified on the basis of the Venn diagram shown in Figure 10.¹⁸ Most agents examined thus far fall into one of several categories. Agents *i*) were “inactive” (e.g. PEA (**1**) – that is, they produced none of these three stimulus effects – perhaps, because they didn’t readily penetrate the BBB at the doses examined, or they produced an altogether different stimulus effect – e.g. morphine and diazepam, *ii*) produced a DOM-like (‘**DOM**’) effect, *iii*) produced an (+)amphetamine-like (‘**AMPH**’) effect, or *iv*) produced a PMMA-like (‘**PMMA**’) effect. Certain agents or isomers produced a combination of effects: a DOM- and PMMA-like (D/P) effect or an (+)amphetamine- and PMMA-like (A/P) effect.

That is, some agents produced more than one stimulus effect based on stimulus generalization studies. MDMA is best characterized as producing an A/P-like effect. ($\pm$)MDA produces all three stimulus effects – that is, ($\pm$)MDA produced stimulus effects best associated with the common (i.e., red) intersect of the Venn diagram (Figure 10). *R*(-)-MDA is a D/P agent, *S*(+)-MDA is a A/P agent. Other agents have been similarly categorized.¹⁸ But, it must be emphasized, as useful as this simple categorization was to initially explain the stimulus actions of certain agents, it was based on the specific training doses of the training drugs employed. And, with the realization that certain of the examined agents have varying effects on SERT, DAT, and/or NET, that likely contribute to, or temper, their actions; a comprehensive understanding of these issues has become more complicated 000251893248251892224 and requires further examination. More will be described below.

11. Ephedrine and Related Phenylpropanolamines

Phenylpropanolamines are β -hydroxy (β -OH) analogs of phenylisopropylamines. *Phenylisopropylamines* (i.e., α -methyl analogs of phenylethylamines) are a class of phenylalkylamines that includes amphetamine (**8**) and methamphetamine (**52**; Figure 11). By introduction of the β -OH function, phenylpropanolamines now possess two chiral centers and four optical isomers are possible (Figure 11). Depending upon stereochemistry, norephedrine is the β -OH analog of amphetamine whereas ephedrine is the β -OH analog of methamphetamine; the other two optical isomers are referred to using the prefix “pseudo” (Figure 11). The naturally-occurring (-)-ephedrine (**53**), the most potent of the phenylpropanolamines as a central stimulant, is several times less potent than amphetamine or methamphetamine.

Phenylalkylamine central stimulants such as amphetamine, methamphetamine, and others readily serve as training drugs in drug discrimination studies and, typically, substitute for one another in tests of stimulus generalization regardless of which agent is used as training drug.¹⁸ This is termed “*cross generalization*”.¹⁸ To investigate phenylpropanolamines more thoroughly, we trained animals to discriminate (-)-ephedrine from vehicle, and (-)-ephedrine-stimulus generalization occurred to (+)-amphetamine; a (+)-amphetamine-stimulus also generalized to (-)-ephedrine – *cross generalization*.¹⁸ We next examined the other phenylpropanolamines shown in Figure 11 and, with the exception of (-)-pseudonorephedrine (**51**) and (-)-pseudoephedrine (**56**), each substituted in (-)-ephedrine-trained animals. The same agents were also examined in (+)-amphetamine-trained animals but stimulus generalization occurred only to (+)-pseudonorephedrine (**49**) and (-)-ephedrine (**53**).⁶² Evidently, although (-)-ephedrine and (+)-amphetamine shared certain stimulus properties, their stimuli are not identical.

As already mentioned, (-)-ephedrine, although several-fold less potent than (+)-amphetamine, was recognized by (+)-amphetamine-trained animals.¹⁸ The reduced potency of the former agent might have been expected on the basis of its lower stimulant potency in humans. However, using animals trained to discriminate (-)-ephedrine from vehicle, stimulus generalization failed to occur upon administration of *S*(+)-methamphetamine.^{18,62} But, *S*(+)-methamphetamine-trained animals (1.0 mg/kg) recognized various phenylalkylamine stimulants including (-)-ephedrine. An *S*(+)-methamphetamine stimulus generalized to

R(-)-methamphetamine ($ED_{50} = 1.61$ mg/kg), *S*(+)-amphetamine ($ED_{50} = 0.28$ mg/kg), and cocaine ($ED_{50} = 3.68$ mg/kg), and (-)-ephedrine ($ED_{50} = 13.1$ mg/kg). Note here that *S*(+)-methamphetamine was 60-fold more potent than cocaine and >200-fold more potent than (-)-ephedrine. Stimulus generalization between *S*(+)-methamphetamine and (-)-ephedrine was not bi-directional (termed: “*asymmetrical generalization*” or “*one-way generalization*”).^{18,63} This can be explained by the two agents producing somewhat similar effects, but that (-)-ephedrine-trained animals are “looking for something else” in addition to the common effect that is being produced – and that this action seems to predominate in (-)-ephedrine-trained animals.

However, upon administration of *R*(-)-methamphetamine (i.e., the less potent central stimulant of the two methamphetamine isomers) to (-)-ephedrine-trained animals, substitution occurred and *R*(-)-methamphetamine ($ED_{50} = 0.9$ mg/kg) was nearly equipotent with (-)-ephedrine ($ED_{50} = 0.8$ mg/kg). It was hypothesized that although the exact basis for the observed results was unclear, they were likely related to the DAT versus NET releasing actions of the agent/isomers with the NET component being predominant.⁶³

We subsequently undertook, in collaboration with Dr. Richard Rothman (NIDA), a thorough investigation of phenylpropanolamine optical isomers and several related agents.⁶⁴ (-)-Ephedrine was examined at a large battery of cloned human receptors and at SERT, DAT, and NET. The most prominent action of ephedrine-type agents was as releasing agents (i.e., as substrates) at NET, followed by their releasing action at DAT.⁶⁴ Stimulus generalization potencies of the agents in (-)-ephedrine-trained animals versus their potency as NET releasing agents was found to be significantly ($r > 0.9$) correlated. However, for a series of 11 agents, potencies as NET and DAT releasing agents were also significantly ($r > 0.9$) correlated.⁶⁴ The question remains as to which transporter, DAT or NET, is primarily responsible for this action, or whether a combination of both is involved. It might be noted, however, that although phenylpropanolamines act both as releasing agents at NET and DAT, they are generally more potent at the former. Interesting, though, was that the only two phenylpropanolamines that substituted in (+)-amphetamine-trained animals were those with the highest potency at DAT (i.e., (+)-pseudonorephedrine (**49**) and (-)-ephedrine).

It might be asked where (-)-ephedrine fits in the Venn diagram shown as Figure 10. This question remains unanswered. Perhaps an additional (A/E; Amphetamine/Ephedrine) domain needs to be added to encompass a noradrenergic (or NET) effect. It can be appreciated that the situation is complex.

The complexity of the stimulus properties of phenylpropanolamines was further demonstrated in studies with caffeine. Methylxanthines such as caffeine are known to potentiate certain (e.g. thermogenic) effects of (-)-ephedrine.⁶⁵ As already mentioned, a (+)-amphetamine stimulus generalized to (-)-ephedrine but not to (+)-ephedrine (**55**). Doses of caffeine that produced 1% drug-appropriate (i.e., vehicle-appropriate) responding when administered alone, potentiated the stimulus effects of (-)-ephedrine when administered in combination to (+)-amphetamine-trained animals.⁶⁶ Furthermore, the (+)-amphetamine stimulus, although it failed to generalize to (+)-ephedrine (**55**), resulted in stimulus generalization when (+)-ephedrine and a saline-like dose of caffeine were administered in

combination. Two agents (at doses that failed to produce a specific stimulus effect) resulted in stimulus generalization when administered in combination. Hence, low doses of caffeine were shown to potentiate the stimulus effects of (-)ephedrine in (+)amphetamine-trained rats, and *altered* the effect of (+)ephedrine such that generalization occurred.⁶⁶

Others had shown that rats trained to discriminate either amphetamine (0.5 mg/kg) or cocaine (10 mg/kg) from vehicle failed to generalize to caffeine, but that stimulus generalization occurred when the animals were administered the “triple combination” of (-)ephedrine, phenylpropanolamine (i.e., a combination of norephedrine isomers) and caffeine.^{67,68} Caffeine also potentiated the discriminative stimulus actions of cocaine in cocaine-trained animals.⁶⁹

Nothing has been reported about the stimulus effects of PEA (1)-caffeine combinations. But, PEA (1) has been used as a training drug in rats,⁷⁰ and its training dose (30 mg/kg) was substantially (i.e., 30 to 60 times) higher than those typically employed for (+)amphetamine. The “level of discriminability was low” (with only about half of the animals reliably learning the task) and it was speculated that PEA (1) was rapidly metabolized by MAO.⁷⁰ Limited tests of stimulus generalization were conducted (and, neither amphetamine nor caffeine was examined).

Nevertheless, there are anecdotal reports of PEA (1) use/abuse. For example, the PEA Forum website⁷¹ suggests human intoxication requires total doses of 1 to 2 to as much as 4 grams, and indicates improved action of PEA (1) when taken with a MAOI. It should be noted that (+)amphetamine produces a stimulant effect in humans at a total dose of 10 to 30 mg. Hence, the active human intoxication dose of PEA (1) is probably >100 times that of (+)amphetamine.

In addition to methylxanthines such as theobromine and caffeine, cocoa powder has been shown to contain PEA (1).⁷² Cocoa powder snuffs are becoming popular for recreational use.⁷¹ But, it is difficult to imagine that the achieved effect (whatever it might be) is due to the behavioral actions of PEA (1), caffeine, of a combination of the two, at the doses administered. Nevertheless, PEA (1)-caffeine combinations require investigation in documented scientific studies.

From the late 1980s into the early 2000s, herbal dietary preparations were very popular and legally available in tablet or capsule form for use in weight reduction (thermogenic agents advertised as “fat burners”) and as “energy boosters”. Many of them contained ephedra, a plant for which (-)ephedrine is a major constituent. Some also contained caffeine (or a caffeine-containing natural product). Because route of administration can influence drug action and/or potency, we questioned whether an orally-administered ephedra-containing product could produce stimulus effects in animals similar to those of a parenterally-administered stimulant. Using rats trained to discriminate (+)amphetamine (i.p.) from vehicle, the (+)amphetamine stimulus generalized to (+)amphetamine administered via the intragastric route, but was about 2.5-fold less potent than via the i.p. route.⁷³ Likewise, (-)ephedrine was also 2.5-fold less potent via the intragastric route compared to the i.p. route. The (+)amphetamine stimulus generalized to intragastric administration of a

commercially available herbal preparation (purchased on the open market); its potency was roughly comparable to what might have been expected on the basis of its reported ephedrine content.⁷³ The results demonstrated that an orally-administered ephedrine-containing herbal preparation could produce a (+)amphetamine-like stimulus effect in animals.⁷³

12. Synthetic Cathinones

(+)Pseudonorephedrine (**49**; Figure 11), also known as (+)cathine – the two agents now realized as being identical, was long considered the active stimulant component of the shrub *Catha edulis*. The leaves of the plant (“*khat*”) have been used (chewed or brewed as a tea) for many hundreds of years in certain Middle Eastern countries. In the late 1970s the United Nations Narcotics Laboratory identified a *phenylpropanonamine*, an optical isomer of cathinone (**57**) (Figure 12), *S*(-)-cathinone, as a khat plant constituent with stimulant potency greater than (+)cathine (reviewed^{74,75}). Our initial work with cathinone was published in 1981, showing that cathinone produced hyperlocomotor effects in mice at relatively low doses (i.e., *S*(-)**57** > (±)**57** > *R*(+)**57**).⁷⁶ Interestingly, our work with cathinone was wholly serendipitous and was begun prior to the discovery of this agent being identified as a constituent of khat. In the course of our studies on phenylalkylamine analogs, we had prepared certain phenylisopropylamines via Friedel-Crafts acylation of substituted benzene precursors followed by α -bromination and subsequent amination. The resultant phenylpropanonamines (or “ β -ketoamphetamines”) were then catalytically reduced (i.e., hydrogenolyzed) to their corresponding phenylisopropylamines. In several instances, we evaluated the phenylpropanonamine synthetic intermediates (now termed cathinone analogs – one of which was ultimately termed “cathinone”) and found some of them active in mouse locomotor assays and, later, in drug discrimination assays using (+)amphetamine-trained animals. During an NIH site visit, the team leader, Dr. Robert Willette (NIDA), who had just returned from a U.N.-sponsored khat conference in Madagascar, informed us that what we had termed β -ketoamphetamine was identical to “cathinone” – the newly-discovered active stimulant component of the khat plant. Once cathinone became a topic of interest, we found ourselves already in possession of substantial information on this substance and several of its aryl-substituted and other analogs.

Cathinone and both of its optical isomers substituted in (+)amphetamine-trained animals (ED_{50} = 0.32, 0.72, and 4.41 mg/kg for *S*(-)- (±)-, and *R*(+)-cathinone, respectively, relative to 0.62 mg/kg for *S*(+)amphetamine) (reviewed⁷⁷). In collaboration with Dr. Marty Schechter (Northeastern Ohio Medical University), using rats trained to discriminate racemic cathinone (ED_{50} = 0.24 mg/kg) from vehicle, stimulus generalization occurred to (+)amphetamine (ED_{50} = 0.20 mg/kg), *S*(-)-cathinone (ED_{50} = 0.22 mg/kg), *R*(+)-cathinone (ED_{50} = 0.72 mg/kg), and (+)cathine (ED_{50} = 1.61 mg/kg).⁷⁷

Cathinone (or we had initially termed β -ketoamphetamine; **57**) was at least as potent as amphetamine as a discriminative stimulus. Some have referred to cathinone as “naturally-occurring amphetamine”. By analogy to N-monomethyl amphetamine (i.e., methamphetamine), we synthesized and examined the N-monomethyl analog of cathinone and termed it *methcathinone* (**58**).^{74,78} Methcathinone was found more potent than cathinone as a locomotor stimulant, and in animals trained to discriminate (+)amphetamine from

vehicle (Table 6). Animals were subsequently trained to discriminate *S*(-)-methcathinone from vehicle⁷⁹ and stimulus generalization occurred to a number of other phenylalkylamine stimulants (some data are provided in Table 6). As was the (+)amphetamine stimulus, the *S*(-)-methcathinone stimulus was potently antagonized by the dopamine D₂ receptor antagonist haloperidol.⁷⁹ *S*(-)-Methcathinone was also a potent synaptosomal releasing agent at DAT and NET (EC₅₀ = 14.8 and 13.1 nM, respectively) with much weaker action at SERT (EC₅₀ = 1,772 nM)⁶⁴ and with a transporter profile similar to that of (+)-amphetamine (Table 5).

Following some additional SAR studies on cathinone analogs, relatively little was published on these agents for over a decade. Then, novel cathinone analogs began to appear of the European clandestine market;⁸⁰ these were termed *synthetic cathinones*.

One of the early synthetic cathinones was referred to as “bath salts”. Bath salts was initially a combination of methylone (MDMC; **59**) – the β-keto analog of MDMA (**43**), mephedrone (**60**), methylenedioxypyrovalerone (MDPV; **61**; Figure 13), or one or more of these agents in combination with other (known or novel) phenylisopropylamines (reviewed^{74,75}). Today, the term “bath salts” is often used rather generically to refer to almost any synthetic cathinone. Over the past 5 or 6 years, approximately 150 different synthetic cathinones have been confiscated from the clandestine market.⁷⁵

On the basis of studies we had conducted with amphetamine-related phenylisopropylamines, as well as with cathinone and methcathinone, we suspected that the synthetic cathinones would behave in a similar manner (i.e., acting primarily as releasing agents at DAT). Mephedrone was, indeed, found to be a DAT/NET releasing agent. However, MDPV was shown by several investigators to be a fairly selective DAT re-uptake inhibitor, with a potency of about 35 to 50 times that of cocaine (reviewed⁷⁴).

Several SAR and QSAR studies have been reported for the synthetic cathinones (reviewed⁷⁵). With regard to those that behaved as releasing agents, the 4-position substituent determined selectivity for DAT versus SERT. Mephedrone (**44**) is the 4-methyl counterpart of methcathinone (**58**). Whereas methcathinone displayed >300-fold selectivity for DAT over SERT (EC₅₀ = 12.5 and 3,860 nM, respectively), mephedrone (EC₅₀ = 49.1 and 118 nM, respectively) displayed only about 2.5-fold selectivity. In contrast, 4-trifluoromethylmethcathinone (EC₅₀ = 2,700 and 190 nM, respectively) was 14-fold selective for SERT. A QSAR study was conducted on a series of seven 4-substituted methcathinone analogs and it was found that as substituent size increased, DAT potency decreased, but SERT potency increased.⁸¹

Because MDPV was the first abused synthetic cathinone that behaved as a DAT re-uptake inhibitor, it was of interest to determine which of its structural features might account for this action. We “deconstructed” the MDPV molecule by the systematic removal of one substituent at a time.⁸² The presence of the carbonyl and methylenedioxy groups made a minimal (10-fold) contribution to potency but had no effect on action (i.e., the *des*-keto and *des*-methylenedioxy analogs of MDPV behaved as DAT reuptake inhibitors). More important contributors were the amine substituent and the extended α side chain. Either a

tertiary amine (or a secondary amine bearing a bulky substituent) or an extended side chain were necessary features for the agents to act as DAT re-uptake inhibitors. The presence of both features, although both were not required, seemed optimal.^{75,82}

One of the compounds examined in the above SAR investigation was **62** (Figure 13) – MDPV minus the methylenedioxy group. While our manuscript describing the above SAR findings was in press,⁸² this agent (α -pyrrolidinovalerophenone or α -PVP) appeared on the clandestine market as “*flakka*”,⁸³ and was popularized in the lay press as the “*zombie drug*”. A subsequent SAR and QSAR investigation of α -PVP analogs showed that the potency of the compounds as synaptosomal DAT re-uptake inhibitors decreased as the length of the α side chain was decreased, that increasing the chain length by an additional methylene group resulted in retention of action and potency (i.e., another agent that appeared on the clandestine market just prior to the publication of our study – under the acronym: “ α -PHP”), that replacement of the *n*-propyl group of **62** with a cyclohexyl moiety doubled potency, and that replacement of the pyrrolidine with a piperidine ring decreased potency several-fold.⁸⁴ For a series of eight analogs, potency as DAT reuptake inhibitors correlated both with α -substituent volume ($r > 0.9$) and lipophilicity ($r > 0.9$); however, for the substituents examined, substituent volume ($\text{\AA}^3$) and lipophilicity (π) were significantly intercorrelated ($r > 0.9$) and it is not known which of these two parameters is the more important.⁸⁴ For a while, we felt we were always just a single step behind clandestine chemists who were making these agents available on the illicit market.

With regard to cathinone analogs that acted as dopamine releasing agents, effects were generally enantioselective with the *S*(-)-isomers being several-fold more potent than their *R*(+) enantiomers. Little was known about the stereochemistry of synthetic cathinones that acted as DAT reuptake inhibitors. After many unsuccessful attempts, the two optical isomers of MDPV were eventually prepared and examined and it was found that *S*(+)MDPV ($\text{IC}_{50} = 2.1 \text{ nM}$) was 180-fold more potent than *R*(-)MDPV, and 100 times more potent than cocaine as a dopamine re-uptake inhibitor.⁸⁵ Although less potent, the same rank order, *S*(+) > ($\pm$) > *R*(-)MDPV was observed for NET reuptake inhibition; both isomers were inactive at SERT as reuptake inhibitors or releasing agents.⁸⁵

As already alluded to,⁷⁴ synthetic cathinones don't represent a pharmacologically homogeneous group of agents. Depending upon terminal amine and aryl substituents, stereochemistry, and the nature of the α side chain, these agents can act as releasing agents or re-uptake inhibitors at DAT, NET, and/or SERT. By “mixing and matching” the various substituents, certain cathinone analogs could possess “mixed” or “hybrid” actions.⁷⁵ This, once again, underscored the concept that small structural alterations to the phenylalkylamine scaffold can have a significant impact on pharmacology.

13. Conformationally-constrained Phenylalkylamines

Many of the agents described herein are drugs of abuse, and nearly all of these phenylalkylamines possess conformationally-flexible side chains. Over the years we have examined various conformationally-constrained analogs of these agents (e.g., amphetamine,

DOM, DOB, MDMA, PMMA).¹⁸ In general, there are two likely means of simple constraint: aminotetralins (**63**) and tetrahydroisoquinolines (**64**) (Figure 14).

For example, the aminotetralin analog of PMMA (i.e., **65**) was at least as potent as its parent in PMMA-trained animals, whereas its tetrahydroisoquinoline counterparts **66** and **67** resulted in vehicle-appropriate responding or incomplete substitution, respectively. Aminotetralin analogs of amphetamine and MDMA also seemed to better account for their actions than their tetrahydroisoquinoline counterparts.¹⁸ However, this does not imply that the latter are without pharmacological action. A tetrahydroisoquinoline analog of MDMA (i.e., TDIQ, **68**) is a case in point.^{86,87} TDIQ resulted in partial generalization when administered to MDMA- or (-)ephedrine-trained animals, and in vehicle-appropriate responding in (+)amphetamine-, DOM-, and PMMA-trained animals. TDIQ also lacked locomotor stimulant actions in mice. To further investigate this agent, rats were trained, and very rapidly learned – more rapidly than any agent we had previously used as a training drug in >20 years – to discriminate TDIQ from vehicle ($ED_{50} = 0.9$ mg/kg).^{86,87} The TDIQ-stimulus failed to generalize to (+)amphetamine, methylphenidate, or PMMA (i.e., the animals responded on the vehicle-appropriate lever), and (-)ephedrine and MDMA administration resulted only in partial generalization. However, the TDIQ-stimulus fully generalized to cocaine ($ED_{50} = 1.5$ mg/kg).⁸⁶ These results were unexpected. (+)Amphetamine, cocaine, and the central stimulant methylphenidate cross-generalize to one another in tests of stimulus generalization.¹⁸ Curiously, TDIQ-trained animals recognized cocaine, but not other stimulants. Tests of stimulus generalization and stimulus antagonism were conducted with a variety of agents, but shed little light on TDIQ's mechanism of action. Additionally, antagonists capable of blocking a cocaine stimulus (e.g. haloperidol) failed to block the actions of TDIQ. A binding profile for TDIQ at 30 receptor populations, as well as at SERT, DAT, and NET, indicated affinity ($K_i < 100$ nM) only for α_{2A} -, α_{2B} -, and α_{2C} -adrenoceptors, suggesting that TDIQ produces its stimulus effects primarily via a non-selective α_2 -adrenoceptor mechanism.⁸⁶ The partial generalization seen between TDIQ, MDMA, and (-)ephedrine might be related to their adrenergic effects and/or to the lack of a dopaminergic/stimulant component of action associated with the latter but absent with TDIQ. It was suggested that TDIQ be examined for the treatment of cocaine abuse.⁸⁶

Because the adrenergic system might be involved in certain forms of anxiety, TDIQ was examined in a mouse object-burying assay (an assay commonly used to evaluate potential anxiolytic agents) and was found to be active.⁸⁸ Compared with other anxiolytic agents (e.g. diazepam, buspirone; **69** and **70**, respectively; Figure 15 – which, incidentally, did not substitute in TDIQ-trained animals), TDIQ was effective in the object-burying assay ($ED_{50} = 0.20, 0.26,$ and 2.36 mg/kg, respectively, for TDIQ, diazepam, and buspirone) but without producing behaviorally-disruptive side effects in a mouse inclined-plane or rotarod assay as seen with the other agents. TDIQ might represent a novel prototype for the development of a new generation of anxiolytic agents.⁸⁸

Here, it was demonstrated that certain conformationally-constrained phenylalkylamines lack many of the actions of their flexible counterparts and open new vistas for further research.

14. 5-HT_{1A} Receptor Ligands

Because the conformationally-constrained phenylalkylamine 8-OH DPAT (**7**) was identified as the first agent to display agonist action and selectivity for 5-HT_{1A} serotonin receptors over all other 5-HT receptors known at the time, it quickly became a very popular pharmacological tool. We examined 8-OH DPAT in DOM-trained animals, before it was found to be a 5-HT_{1A} receptor agonist, and observed a lack of generalization. We later trained animals to discriminate 8-OH DPAT from vehicle in order to investigate its SAR and mechanism of action and, later, in an attempt to develop a 5-HT_{1A} receptor antagonist, of which none was then available.⁸⁹

8-OH DPAT-trained animals did not recognize DOM which, by this time, had been shown to be a 5-HT₂ receptor agonist. The 8-OH DPAT stimulus generalized to its shorter N,N-diethyl counterpart **73** (Figure 16), but not to its N,N-dimethyl analog **72** or longer N,N-di-*n*-butyl homolog **74**.^{18,89} Results with the 8-OH DPAT analogs were consistent with 5-HT_{1A} binding data: K_i = 4.84 nM, 9.65 nM, 75 nM, and 109 nM for **7**, **73**, **72**, and **74**, respectively (for their *R*-isomers).⁹⁰ That is, only the highest affinity agent, **73**, substituted in the 8-OH DPAT-trained animals. [The *R*(+)-isomers displayed several-fold higher affinity than their *S* enantiomers except for **74** where the *S*-isomer possessed twice the affinity of the *R*.]⁹⁰ It was suspected that increased bulk on the terminal amine was not well tolerated by the receptor.⁹⁰

It was demonstrated (using radioligand binding and drug discrimination studies) that the hydroxyl group of 8-OH DPAT (**7**) could be replaced by a methoxy group (5-HT_{1A} K_i = 1.2 and 1.3 nM, respectively, for **7** and **75**) (Table 7).⁹¹ This was significant in that 8-methoxy analogs were more convenient to synthesize than their corresponding phenols and, in theory, should possess better BBB permeability than 8-OH DPAT itself (which, early on, was a consideration that later proved to be unfounded).

Using Ariens' concept of *accessory receptor areas*⁹² whereby introduction of a bulky terminal amine group often converts an agonist to an antagonist, we prepared several amine-substituted compounds (Table 7). It was fairly evident that both *n*-propyl groups were not required for high-affinity binding. 3-(Phenyl)propyl compounds **79** and **80** displayed affinities nearly comparable to **75** and 8-OH DPAT. To determine if extended bulk was allowed here but not with, for example, **74**, because these compounds possessed a methoxy rather than 8-OH group, we examined the O-*des*-methyl counterpart of **80** and found it to bind (K_i = 1.9 nM) with similar affinity.⁹¹ Unfortunately, the functional activities of these analogs (except for **75**) were never examined because we had just identified NAN-190 (**71**) as a 5-HT_{1A} receptor antagonist in a series of companion studies, and turned our attention in that direction (see later). But, it was learned that both 8-OH DPAT *n*-propyl substituents were not required for 5-HT_{1A} receptor binding, that the primary amine binds with substantially reduced affinity compared to 8-OH DPAT (**7**) and **75**, and that an *n*-propyl group could be replaced with a 3-(phenyl)propyl group without significant loss of affinity. These types of compounds remain to be further investigated, and might yet yield novel 5-HT_{1A} receptor antagonists.

8-OH DPAT is a conformationally-constrained phenylalkylamine. Interestingly, release of the conformational constraint resulted in a several hundred-fold reduction in HT_{1A} receptor affinity. For example, phenylethylamine **82** (Figure 16), as well as its mono-N-*n*-propyl counterpart, bind with $K_i = 400$ nM and $>1,000$ nM, respectively.⁹³ This dramatic decrease in affinity has never been explained.

There was literature evidence at the time that 8-OH DPAT produced an anxiolytic effect in rodents. Hence, we examined several anxiolytic agents (e.g. diazepam; **69**) and found that they failed to substitute in 8-OH DPAT trained animals.¹⁸ It might be noted that we had earlier examined diazepam as a training drug and were well acquainted with its stimulus actions and the SAR of benzodiazepines in this regard.¹⁸ However, buspirone (**70**) substituted in a dose-dependent fashion in 8-OH DPAT-trained animals, and this was the first indication that this novel (at that time) anxiolytic agent might be acting through a 5-HT_{1A} receptor agonist mechanism. Currently, the anxiolytic action of buspirone is recognized as being attributable to a 5-HT_{1A} partial agonist mechanism.¹⁸ As a side note, diazepam-trained animals did not recognize 8-OH DPAT, and buspirone-trained animals failed to recognize diazepam.¹⁸ Continued investigations using 8-OH DPAT-trained animals ultimately resulted in one of the first useful 5-HT_{1A} receptor antagonists: NAN-190 (**71**).¹⁹

15. “Candy Flipping”

During the course of our investigations with DOM, we found that very low doses of the 5-HT_{1A} receptor agonist 8-OH DPAT potentiated DOM stimulus effects, and that administration of the ED₅₀ dose of DOM in combination with 8-OH DPAT doses resulted in complete stimulus generalization in DOM-trained animals. It should be noted that neither agent substituted for the other in tests of stimulus generalization, and that DOM lacks affinity for 5-HT_{1A} receptors and 8-OH DPAT lacks affinity for 5-HT₂ receptors. The mechanism underlying this potentiation is not yet fully understood.

Administration of our 5-HT_{1A} receptor antagonist NAN-190 (**71**) to MDMA-trained animals had no effect (i.e., no stimulus generalization); however, when administered in combination with the MDMA training dose, partial antagonism occurred. MDMA is known to release 5-HT and the released 5-HT can interact with any of several populations of 5-HT receptors including 5-HT_{1A} receptors. Subsequently, and somewhat unexpectedly, in tests of stimulus generalization MDMA-trained animals generalized to 8-OH DPAT and both of its optical isomers.¹⁸ It has been demonstrated in various assays that *R*(+)-8-OH DPAT is a full agonist at 5-HT_{1A} receptors whereas *S*(-)-8-OH DPAT is a partial agonist; in general, both isomers can produce 8-OH DPAT-like effects, but the *R*(+)-isomer is several times more potent.⁹⁰ In the MDMA-trained animals, stimulus generalization occurred with the following rank order of potency: *R*(+)- > (±) > *S*(-)-8-OH DPAT.⁹⁴ Hence, the 5-HT releasing actions of MDMA, at least in drug discrimination studies, might be due, to a large extent, to activation of 5-HT_{1A} receptors.

The phenomenon known as “*flipping*” or “*candy flipping*” refers to the combined use of a classical hallucinogen plus MDMA to achieve a heightened effect by drug users. That is, the combination seemingly results in a synergistic effect. Given that 8-OH DPAT potentiated the

stimulus actions of DOM, and that an MDMA-stimulus generalized to 8-OH DPAT, it was not unreasonable to hypothesize that MDMA might potentiate the stimulus actions of DOM – and, as such – represent an animal counterpart of “candy flipping”. First, it was demonstrated that *R*(+)-8-OH DPAT was twice as potent as (±)-8-OH DPAT in potentiating the stimulus effects of DOM (i.e., both agents in combination with the DOM ED₅₀ dose resulted in stimulus generalization in DOM-trained animals). Next, it was shown that NAN-190 was capable of blocking this effect (but not the effect of DOM when administered alone). And lastly, it was shown that low doses of MDMA potentiated the ED₅₀ dose of DOM to result in DOM-stimulus generalization.⁹⁵ More recently, it has been reported that 8-OH DPAT (**7**) is also a 5-HT₇ receptor agonist. However, NAN-190 does not bind at 5-HT₇ receptors and this latter population is unlikely to account for the potentiating effect that was described above.¹⁸

16. Sigma Receptor Ligands

Sigma (σ) receptor research got off to an arduous beginning, but even early efforts hinted at a relationship between σ receptors and stimulant abuse (reviewed^{96,97}). One of the first agents found to bind at σ receptors was *N*-allylnormetazocine (NANM; **83**) (Figure 17) (reviewed⁹⁸). It might be noted that **83** has embedded within its structure a phenylethylamine moiety and, more specifically, an amphetamine (**8**) moiety. We deconstructed NANM to determine the various structural features important for σ receptor binding (reviewed^{98,99}). Using tritiated ditolylguanidine ([³H]DTG), various deconstructed analogs of NANM were examined. One of these, (+)-amphetamine, displayed very low affinity (K_i = 46,000 nM) relative to (±)-NANM and its higher-affinity isomer (+)-NANM (K_i = 430 and 150 nM, respectively).⁹⁹ However, we eventually prepared several amine-substituted analogs of amphetamine that resulted in >2,000-fold enhanced affinity (e.g. **84** and **85**; K_i = 22 and 6.3 nM, respectively for their *S*(+) isomers).⁹⁹ Aryl substitution and stereochemistry seemed to play little to no role in the binding of **84** and **85** analogs.⁹⁹

In rats trained to discriminate (+)-NANM from vehicle, *R*(-)-**84** (σ K_i = 28 nM), and several related analogs, behaved as effective NANM antagonists.¹⁰⁰

Shortly thereafter, two populations of σ receptors were identified: σ_1 and σ_2 receptors. Using [³H](+)-pentazocine to label σ_1 receptors, **85** displayed higher affinity (K_i = 0.9 and 0.5 nM for *S*(+)- and *R*(-)-**85**, respectively) than they did for the undifferentiated σ receptors. N-Methylation was found to have a small affinity-enhancing effect, and the affinity of **86** (K_i = 0.25 nM) was slightly higher than that of **85**. Interestingly, replacement of the phenylethylamine aryl ring of **86** with a methyl group had no effect on affinity (**87**; K_i = 0.29 nM), whereas a parallel replacement of the opposing aryl group decreased affinity by nearly 200-fold (**88**; K_i = 48 nM).¹⁰¹ Evidently, the presence of the 5-(phenyl)pentyl moiety, although still an arylalkylamine, was more consequential than the phenylethylamine portion. Phenylethylamine **89** (K_i = 0.14 nM) also displayed high affinity. Retention of a phenylethylamine structure, as in **90** (K_i = 0.08 nM), was tolerated but, here too, was unnecessary (**91** and **92**; K_i = 0.38 and 0.07 nM, respectively).^{99,101}

Eventually, we went on to examine other piperidine and piperazine analogs, identified a pharmacophore for σ_1 receptor binding, and turned our attention to σ_1 versus σ_2 selectivity.^{99,101} A σ_2 receptor pharmacophore was later identified.¹⁰² Nevertheless, this is a stunning example of how a phenylethylamine with mid- μ M affinity for σ receptors (i.e., **8**) was structurally manipulated to result in a >100,000-fold increase in affinity.

17. 5-HT₆ Receptor Ligands

We developed 5-methoxy-*N,N*-dimethyl-*N*₁-benzenesulfonyltryptamine (MS- 245; **93**) (Figure 18) as one of the first 5-HT₆ receptor antagonists (reviewed¹¹³). Frantz et al.¹⁰⁴ demonstrated that the 5-HT₆ receptor antagonist SB 258510A enhanced certain actions of amphetamine (e.g. rat locomotor activity, self-administration) but not those of cocaine. Likewise, we found that MS-245 was without effect when administered to rats trained to discriminate (+)amphetamine from vehicle in a drug discrimination task, but potentiated the stimulus effects of the training drug such that MS-245 administered in combination with the ED₅₀ dose of (+)amphetamine, stimulus generalization occurred.¹⁰⁵ Similar studies were conducted using rats trained to discriminate cocaine from vehicle, but a combination of the ED₅₀ dose of cocaine together with doses of MS-245 resulted in no potentiation. Furthermore, although MS-245 neither substituted for nor antagonized the discriminative stimulus effects of (-)nicotine, it was shown to enhance the potency of (-)nicotine in animals trained to discriminate (-)nicotine from vehicle. That is, a combination of the ED₅₀ dose of (-)nicotine plus MS-245 resulted in stimulus generalization.¹⁰⁶ MS-245 also potentiated the hypolocomotor actions, but not the antinociceptive effects, of (-)nicotine in mice.¹⁰⁶ Taken together, the data suggested that 5-HT₆ serotonin receptor agents might have potential clinical application in therapies that involve modulation of dopamine neurotransmission, or in the treatment of certain aspects of drug abuse. It was findings, such as these that were partly responsible for our continued interest in this area.

Benz[c,d]indole **94** (K_i = 1.6 nM) displayed an affinity similar to that of MS-245 (K_i = 2.1 nM). Conversion to aminotetralin **95** and phenylethylamine **96** (K_i = 49 and 21 nM, respectively) resulted in reduced affinity but identified novel chemotypes for exploitation. For example, **97**, the “reverse sulfonamide” of **96**, and sulfone **98**, both displayed modest affinity (K_i = 70 and 50 nM). Transposition of these functionalities to the phenylethylamine 4-position also resulted in interesting compounds such as, for example, sulfonamide **99** (K_i = 38 nM) and “reverse sulfonamide” **100** (K_i = 2.5 nM).¹⁰³ Again, examples of phenylethylamines with an unanticipated action.

18. α -ET

As an extension of some of the topics/concepts described above, this final section deals with several arylalkylamine (i.e., indolealkylamine or tryptamine) drugs of abuse. Although not phenylalkylamines, the behavioral effects of many indolealkylamines, such as 5-OMe DMT (**7**) and numerous other *N,N*-dialkyltryptamines, were examined in our studies (reviewed¹⁸). As alluded to earlier regarding *phenylalkylamines*, *indolealkylamines* typically conjure tryptamine analogs where an indole nucleus is separated from a terminal amine by a two-atom carbon unit. Many such analogs were investigated using drug discrimination studies

with animals trained to discriminate DOM.¹⁸ We also examined gramine analogs, homotryptamines, and isotryptamines. Here, we address several “*α-alkyl tryptamines*”. Both *α*-methyltryptamine (*α*-MeT, AMT, “Spirals”; **101**) and its homolog, *α*-ethyltryptamine (*α*-ET, AET, “ET”; **102**), have been found on the clandestine market since the 1960s as abused substances. Nearly 35 years ago¹⁰⁷ we showed that both of these agents, as their racemates ($ED_{50} = 3.1$ and 6.6 mg/kg for **101** and **102**, respectively), substituted in tests of stimulus generalization using DOM-trained animals (for comparison: DOM $ED_{50} = 0.44$ mg/kg). Furthermore, although *S*(+)*α*-MeT ($ED_{50} = 1.64$ mg/kg), but not *R*(-)*α*-MeT, fully substituted for DOM, only the racemate was available on the clandestine market.

α-MeT displayed modest affinity for [³H]ketanserin-labelled 5-HT₂ receptors ($K_i = 3,100$ nM), and *S*(+)*α*-MeT ($K_i = 2,500$ nM) displayed slightly higher affinity than *R*(-)*α*-MeT ($K_i = 5,000$ nM).¹⁰⁸ Hence, it was not unreasonable to assume that *α*-MeT might be acting as a classical hallucinogen, but with modest potency.

In humans, *α*-ET purportedly produces relatively weak hallucinogenic and central stimulant actions. DOM-trained animals recognized *α*-ET (Table 8); however, when administered to (+)amphetamine-trained animals, only partial generalization occurred.¹⁰⁹ Because *α*-ET possesses a chiral center, both optical isomers were prepared and individually examined (Table 8). Reminiscent of what was seen with MDA, one *α*-ET isomer, the *S*(+)isomer, substituted in DOM- but not in (+)amphetamine-trained animals whereas the other, the *R*(-)isomer, substituted in (+)amphetamine- but not DOM-trained animals (Table 8).¹¹⁰ It appeared that the two optical isomers were capable of producing different stimulus actions. Given our prior experience with MDA, the results looked familiar.

Subsequent studies showed that *α*-ET produced MDMA-like stimulus effects (Table 8). It was looking more and more like *α*-ET was an indolealkylamine counterpart of MDA.

Later, animals were trained to discriminate racemic *α*-ET from vehicle,¹¹³ and greater than one year of training was required to establish the stimulus cue (see comments in Section 10 on training animals to discriminate MDA from vehicle). *α*-ET stimulus generalization occurred to PMMA and DOM, and partial generalization was seen with (+)amphetamine (Table 8). Taken together, the results indicated that *S*(+)*α*-ET was, primarily, a DOM-like agent, *R*(-)*α*-ET was more of a (+)amphetamine-like agent, and that both isomers produced a PMMA-like effect. The results are noteworthy because they showed that the stimulus effects of certain indolalkylamines, as well as phenylalkylamines, might be explained by the Venn diagram depicted in Figure 10.

What underlies the stimulus actions of *α*-ET? Again in a collaborative effort with Dr. Rothman (NIDA), it was found that *α*-ET isomers behaved differently as releasing agents at SERT, DAT, and NET; EC_{50} values for *S*(+)*α*-ET and *R*(-)*α*-ET were 20 and 68 nM, at SERT, and 64 and 900 nM at DAT, respectively, and >10,000 at NET.¹⁸ Blough et al.,¹¹⁴ at nearly the same time, published similar findings: EC_{50} values for *S*(+)*α*-ET and *R*(-)*α*-ET were 35 and 55 nM at SERT, and 55 and 654 nM at DAT, but showed higher potency at NET (592 and 3,670 nM, respectively) even though still reduced compared to potency at SERT

and DAT. *S*(+)- α -ET was also demonstrated to act as a weak 5-HT_{2A} receptor partial agonist in a calcium mobilization assay whereas *R*(-)- α -ET was inactive.¹¹⁴

The results of the drug discrimination studies were, to some extent, counterintuitive. Curiously, the 5-HT releasing agent fenfluramine (**103**), an agent not generally considered to be hallucinogenic, has been shown to substitute in DOM-trained animals.¹⁰⁹ This phenomenon has never been fully explained. Fenfluramine, in addition to being a weak 5-HT_{2A} partial agonist, is a releasing agent at SERT (EC₅₀ = 108 nM) and NET (EC₅₀ = 740 nM), but inactive at DAT. Its actions are not unlike those of MDMA (EC₅₀ = 72, 110, and 278 nM for SERT, NET, and DAT, respectively; Table 5) except that MDMA is more potent than fenfluramine at DAT.^{59,115} Hence, the actions of *S*(+)- α -ET might be related to its weak agonist action at 5-HT_{2A} receptors coupled with possible potentiation by release at SERT (see also Section 15 on “Candy Flipping”). The actions of *R*(-)- α -ET are more of a conundrum; being a weaker releaser at DAT than its *S*(+)-enantiomer, it is difficult to explain why stimulus generalization occurred; nevertheless, it might be noted that it was approximately 20 times less potent than (+)amphetamine (Table 8).

Bottom line: the actions of certain indolealkylamines, especially α -substituted tryptamines, *i*) can be as complex as some phenylalkylamines already discussed, and *ii*) lend themselves to possible classification as described in Figure 10. Considerable effort has been devoted by many investigators to study the behavioral and mechanistic character of phenylalkylamine drugs of abuse (e.g. central stimulants, hallucinogens, empathogens). It would seem that more work now needs to be done with other arylalkylamines, such as indolalkylamines – specifically, tryptamines and α -substituted tryptamines.

19. Summary

The purpose of this review was to extoll the ubiquity and utility of the simple, chameleon-like, phenylalkylamine motif, to provide examples of how relatively minor structural modifications immensely impact its pharmacology, and to highlight some of our efforts in these areas with a particular emphasis on drugs of abuse. It was the latter studies that opened new avenues of pursuit to us (e.g. 5-HT_{1A}, 5-HT₆, and other receptors).

The phenylethylamine moiety has risen from humble beginnings as a presumed metabolic by-product to serve as a noteworthy scaffold for therapeutically useful agents, and for an even greater number of abused substances. PEA (**1**) even has its own, although shared, receptor – TAAR1 – and seems to play a role as a neuromodulator. TAARs are deserving of additional study. PEA (**1**) is not centrally active via common routes of administration unless heroic doses are consumed/employed. However, introduction of substantive structural appendages to PEA (**1**) results in agents with a wide variety of actions (e.g. see Figure 2 and the related discussion). Of perhaps greater note is that even relatively minor structural changes to the PEA (**1**) molecule have significant pharmacological impact. The simple introduction of phenolic/benzylic hydroxyl groups leads to the major neurotransmitters dopamine and norepinephrine. Introduction of other simple substituents enhance its lipophilicity to increase its BBB penetrability, or alter its actions. For example, appending an α -methyl group to PEA (**1**) leads to the phenylisopropylamine stimulant amphetamine.

Then, structural alteration of the amphetamine structure leads to a host of other actions. Introduction of certain aryl substituents converts amphetamine to classical hallucinogens that act via a 5-HT₂ receptor agonist mechanism, whereas other substituents result in 5-HT₂ receptor antagonists. Different aryl, side chain, and amine substituents result in central stimulants, empathogens, 5-HT_{1A} receptor agonists, and agents with therapeutic potential. Stereochemistry plays a role when the side chain bears substituents. Conformational aspects are also important.

Many of the agents discussed here have been demonstrated to produce discriminative stimuli in animals that are helpful in their behavioral classification and characterization and that variously act at 5-HT₂ and 5-HT_{1A} serotonin receptors, adrenoceptors, and at monoamine transporters (SERT, DAT, NET) and, at the latter, as releasing agents and/or as re-uptake inhibitors, and occasionally, with different selectivities. Many of the agents are abused substances, others possess mechanistic attributes that (internally – SERT vs DAT action of a given agent) temper, or potentiate (i.e., 8-OH DPAT), these actions, and the actions of some agents probably involve multiple mechanisms. However, the potential for specific agents acting by a combination of these mechanisms represents nuances that require further investigation. Nevertheless, it is rather astounding how relatively minor structural changes on a very simple Ph-C-C-N molecule have such a profound influence on its actions. Hence, the “phenylalkylaminegnome”.

The abuse of *designer drugs* is a terrible (and costly) societal scourge, and these agents are appearing in unprecedented numbers, and faster than they can be controlled (i.e., Scheduled) or treatments identified. The term “designer drug” has not been used here so far. But, many of the agents currently appearing on the clandestine market are “designer drugs”, and most of them possess an arylalkylamine or phenylalkylamine backbone. Recently, the term “*novel psychoactive substances*” (NPS) has been coined; and, these NPS include, for the most part, novel phenylalkylamines, especially, phenylalkylamine hallucinogens and phenylpropanonamines (i.e. synthetic cathinones). Studies such as those described here, as well as those of other investigators, attempt to unlock the mechanism(s) of action of these agents so that effective treatments might be identified for their abuse, and to provide data that can be used in forecasting and controlling agents that have yet to appear on the clandestine market.

Acknowledgments

Most of the drug abuse-related studies from the author's laboratory were supported by NIDA grants DA-01642 (receptor binding and drug discrimination studies involving hallucinogens, central stimulants, and cathinone/methcathinone analogs) and DA-33930 (new “synthetic cathinones”). Some studies were supported by NIMH grant MH-60599 (various serotonergic agents including development of NAN-190). Other studies mentioned here were supported, in part, by funding from Cambridge Neuroscience (sigma receptors), Alcon (glaucoma studies), Allelix Biopharmaceuticals (early 5-HT₆ and other studies), and the British Technology Group (later 5-HT₆ receptor and other studies). The author wishes to thank his graduate students, postdoctoral fellows, laboratory assistants, and collaborators (who shared co-authorship of many of the papers cited here). In particular, collaborators Dr. Richard Young and Dr. Małgorzata Dukat deserve special recognition for their critical scientific input and assistance with many of these studies.

References

1. Glennon, RA. The Phenylalkylaminome: Scaffolding for drugs of abuse, with a focus on synthetic cathinones. Abstract MEDI 250. 249th American Chemical Society National Meeting & Exposition; Denver, Colorado. March 2015;
2. Wishart DS, Knox C, Guo AC, Shrivastava S, Hassanali M, Stothard P, Chang Z, Woolsey J. DrugBank: A comprehensive resource for in silico drug discovery and exploration. *Nucleic Acids Res.* 2006; 34(Database issue):D668–672. [PubMed: 16381955]
3. Grandy DK. Trace amine-associated receptor 1 – Family archetype or iconoclast? *Pharmacol Ther.* 2007; 116:355–390. [PubMed: 17888514]
4. Irsfeld M, Spadafore M, Prüß BM. β -Phenylethylamine, a small molecule with a large impact. *Webmedcentral.* 2013; 4 pii: 4409.
5. Berry MD. Mammalian central nervous system trace amines. Pharmacologic amphetamines, physiologic neuromodulators. *J Neurochem.* 2004; 90:257–271. [PubMed: 15228583]
6. Pei Y, Asif-Malik A, Canales JJ. Trace amines and the trace amine-associated receptor 1: Pharmacology, neurochemistry, and clinical implications. *Front Neurosci.* 2016; 10:148.doi: 10.3389/fnins.2016.00148 [PubMed: 27092049]
7. Wood PL, Pilapil C, LaFaille F, Nair NP, Glennon RA. Unique [3 H]tryptamine binding sites in rat brain: Distribution and pharmacology. *Arch Int Pharmacodyn Ther.* 1984; 268:194–200. [PubMed: 6732364]
8. Usdin, E., Sandler, M., editors. *Trace Amines and the Brain.* M. Dekker; New York: 1976.
9. Branchek TA, Blackburn TP. Trace amine receptors as targets for novel therapeutics: Legend, myth and fact. *Curr Opin Pharmacol.* 2003; 3:90–97. [PubMed: 12550748]
10. Lindemann L, Hoener MC. A renaissance in trace amines inspired by a novel GPCR family. *Trends Pharmacol Sci.* 2005; 26:274–281. [PubMed: 15860375]
11. Borowsky B, Adham N, Jones KA, Raddatz R, Artymyshyn R, Ogozalek KL, Durkin MM, Lakhani PP, Bonini JA, Pathirana S, Boyle N, Pu X, Kouranova E, Lichtblau H, Ochoa FY, Branchek TA, Gerald C. *Proc Nat Acad Sci (US).* 2001; 98:8966–8971.
12. Bunzow JR, Sonders MS, Arttamangkul S, Harrison LM, Zhang G, Quigley DI, Darland T, Suchland KL, Pasumamula S, Kennedy JL, Olson SB, Magenis RE, Amara SG, Grandy DK. Amphetamine, 3,4-methylenedioxymethamphetamine, lysergic acid diethylamide, and metabolites of the catecholamine neurotransmitters are agonists of a rat trace amine receptor. *Mol Pharmacol.* 2001; 60:1181–1188. [PubMed: 11723224]
13. Zucchi R, Chiellini G, Scanlan TS, Grandy DK. Trace amine-associated receptors and their ligands. *Br J Pharmacol.* 2006; 149:967–978. [PubMed: 17088868]
14. Lewandowsky M. Zur lehre von der cerebrospinalflüssigkeit. *Z Klin Med.* 1900; 40:480–494. as cited in: Hawkins BT, Davis TP. The blood-brain barrier. *Pharmacol Rev.* 2005; 57:173–718. [PubMed: 15914466]
15. Pardridge WM. The blood-brain barrier: Bottleneck in brain drug development. *J Am Soc Exp NeuroTherapeutics.* 2005; 2:3–14.
16. Hollister, LE. *Chemical Psychosis.* Charles C. Thomas; Springfield Illinois: 1968.
17. Glennon, RA. Animal models for assessing hallucinogenic agents. In: Boulton, A.Baker, G., Wu, P., editors. *Animal Models of Drug Addiction.* Humana Press; Totowa, NJ: 1992. p. 345–381.
18. Glennon, RA., Young, R. *Drug Discrimination: Applications to Medicinal Chemistry and Drug Studies.* Wiley; Hoboken: 2011.
19. Glennon RA, Naiman NA, Pierson ME, Titeler M, Lyon RA, Weisberg E. NAN-190: An arylpiperazine analog that antagonizes the stimulus effects of the 5-HT_{1A} agonist 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT). *Eur J Pharmacol.* 1988; 154:339–341. [PubMed: 2976673]
20. Young R, Rosecrans JA, Glennon RA. Behavioral effects of 5-methoxy-*N,N*-dimethyltryptamine and dose-dependent antagonism by BC-105. *Psychopharmacology (Berlin).* 1983; 80:156–160. [PubMed: 6410445]
21. Young R, Glennon RA. Discriminative stimulus properties of amphetamine and structurally related phenalkylamines. *Med Res Rev.* 1986; 6:99–130. [PubMed: 3512936]

22. Gaddum JH, Hameed KA. Drugs which antagonize 5-hydroxytryptamine. *Br J Pharmacol Chemother.* 1954; 9:240–248. [PubMed: 13172437]
23. Glennon, RA. The role of serotonin in the mechanism of action of hallucinogenic agents. In: Green, AR., editor. *Neuropharmacology of Serotonin*. Oxford University Press; 1985. p. 253-280.
24. Peroutka SJ, Snyder SH. Multiple serotonin receptors: Differential binding of [³H]5-hydroxytryptamine, [³H]lysergic acid diethylamide and [³H]spiroperidol. *Mol Pharmacol.* 1979; 16:687–699. [PubMed: 530254]
25. Cohen ML, Wittenauer LA. Relationship between serotonin and tryptamine receptors in the rat stomach fundus. *J Pharmacol Exp Ther.* 1985; 233:75–79. [PubMed: 3981465]
26. Wainscott DB, Cohen ML, Schenck KW, Audia JE, Nissen JS, Baez M, Kursar JD, Lucaites VL, Nelson DL. Pharmacological characteristics of the newly cloned rat 5-hydroxytryptamine_{2F} receptor. *Mol Pharmacol.* 1993; 43:419–426. [PubMed: 8450835]
27. Nelson DL, Lucaites VL, Wainscott DB, Glennon RA. Comparisons of hallucinogenic phenylisopropylamine binding affinities at cloned human 5-HT_{2A}, 5-HT_{2B} and 5-HT_{2C} receptors. *Naunyn-Schmiedeberg's Arch Pharmacol.* 1999; 359:1–6. [PubMed: 9933142]
28. Glennon, RA., Dukat, M. Serotonin receptors and drugs affecting serotonergic neurotransmission. In: Lemke, T. Williams, DA. Roche, VF., Zito, SW., editors. *Foye's Textbook of Medicinal Chemistry*. Wolters Kluwer / Lippincott Williams & Wilkins; Baltimore, MD: 2013. p. 365-396.
29. Glennon RA, Dukat M, Grella B, Hong SS, Costantino L, Teitler M, Smith C, Egan C, Davis K, Mattson MV. Binding of β -carbolines and related agents at serotonin (5-HT₂ and 5-HT_{1A}), dopamine (D₂) and benzodiazepine receptors. *Drug Alcohol Depend.* 2000; 60:121–132. [PubMed: 10940539]
30. Glennon, RA. Classical Hallucinogens. In: Schuster, CR., Kuhar, MJ., editors. *Handbook of Experimental Pharmacology: Pharmacological Aspects of Drug Dependence*. Springer Verlag; Basel, Switzerland: 1996. p. 343-371.
31. Leysen JE, Awouters F, Kennis L, Laduron PM, Vandenberk J, Janssen PA. Receptor binding profile of R 41 468, a novel antagonist at 5-HT₂ receptors. *Life Sci.* 1981; 28:1015–1022. [PubMed: 6261070]
32. Colpaert FC, Niemegeers CJ, Janssen PA. A drug discrimination analysis of lysergic acid diethylamide (LSD): in vivo agonist and antagonist effects of purported 5-hydroxytryptamine antagonists and of pirenperone, a LSD-antagonist. *J Pharmacol Exp Ther.* 1982; 221:206–214. [PubMed: 7062283]
33. Glennon RA, Young R, Rosecrans JA. Antagonism of the effects of the hallucinogen DOM and the purported 5-HT agonist quipazine by 5-HT₂ antagonists. *Eur J Pharmacol.* 1983; 91:189–196. [PubMed: 6617740]
34. Vollenweider FX, Vollenweider-Scherpenhuyzen MF, Bähler A, Vogel H, Hell D. Psilocybin induces schizophrenia-like psychosis in humans via a serotonin-2 agonist action. *Neuroreport.* 1998; 9:3897–3902. [PubMed: 9875725]
35. Quednow BB, Komater M, Geyer M, Vollenweider FX. Psilocybin-induced deficits in automatic and controlled inhibition are attenuated by ketanserin in healthy human volunteers. *Neuropsychopharmacology.* 2012; 37:630–640. [PubMed: 21956447]
36. Komater M, Schmidt A, Jäncke L, Vollenweider FX. Activation of serotonin 2A receptors underlies the psilocybin-induced effects on α . oscillations, N170 visual-evoked potentials, and visual hallucinations. *J Neurosci.* 2013; 33:10544–10551. [PubMed: 23785166]
37. Seggel MR, Yousif MY, Lyon RA, Titeler M, Roth BL, Suba EA, Glennon RA. A structure-affinity study of the binding of 4-substituted analogues of 1-(2,5-dimethoxyphenyl)-2-aminopropane at 5-HT₂ serotonin receptors. *J Med Chem.* 1990; 33:1032–1036. [PubMed: 2308135]
38. Titeler M, Lyon RA, Glennon RA. Radioligand binding evidence implicates the brain 5-HT₂ receptor as a site of action for LSD and phenylisopropylamine hallucinogens. *Psychopharmacology (Berlin).* 1988; 94:213–216. [PubMed: 3127847]
39. Glennon RA, Seggel MR, Soine WH, Herrick-Davis K, Lyon RA, Titeler M. [¹²⁵I]-1-(2, 5-Dimethoxy-4-iodophenyl)-2-aminopropane: An iodinated radioligand that specifically labels the agonist high-affinity state of 5-HT₂ serotonin receptors. *J Med Chem.* 1988; 31:5–7. [PubMed: 3336031]

40. Rangisetty JB, Dukat M, Dowd CS, Herrick-Davis K, DuPre A, Gadepalli S, Teitler M, Kelley CR, Sharif NA, Glennon RA. 1-[2-Methoxy-5-(3-phenylpropyl)]-2-aminopropane unexpectedly shows 5-HT_{2A} serotonin receptor affinity and antagonist character. *J Med Chem*. 2001; 44:3283–3291. [PubMed: 11563927]
41. Dowd CS, Herrick-Davis K, Egan C, DuPre A, Smith C, Teitler M, Glennon RA. 1-[4-(3-Phenylalkyl)phenyl]-2-aminopropanes as 5-HT_{2A} partial agonists. *J Med Chem*. 2000; 43:3074–3084. [PubMed: 10956215]
42. Glennon RA, Titeler M, Seggel MR, Lyon RA. N-Methyl derivatives of the 5-HT₂ agonist 1-(4-bromo-2,5-dimethoxyphenyl)-2-aminopropane. *J Med Chem*. 1987; 30:930–932. [PubMed: 3572981]
43. Eckler JR, Chang-Fong J, Rabin RA, Smith C, Teitler M, Glennon RA, Winter JC. Behavioral characterization of 2-O-desmethyl, and 5-O-desmethyl metabolites of the phenylethylamine hallucinogen DOM. *Pharmacol Biochem Behav*. 2003; 75:845–852. [PubMed: 12957227]
44. Jacob P. 3rd, Kline, T., Castagnoli, N. Jr. Chemical and biological studies of 1-(2,5-dihydroxy-4-methylphenyl)-2-aminopropane, an analogue of 6-hydroxydopamine. *J Med Chem*. 1979; 22:662–671. [PubMed: 458821]
45. Glennon RA, Bondarev ML, Khorana N, Young R, May JA, Hellberg MR, McLaughlin MA, Sharif NA. β -Oxygenated analogues of the 5-HT_{2A} serotonin agonist 1-(4-bromo-2,5-dimethoxyphenyl)-2-aminopropane. *J Med Chem*. 2004; 47:6034–6041. [PubMed: 15537358]
46. May JA, Sharif NA, Chen HH, Liao JC, Kelly CR, Glennon RA, Young R, Li JX, Rice KC, France CP. Pharmacological properties and discriminative stimulus effects of a novel and selective 5-HT₂ receptor agonist AL-38022A [(S)-2-(8,9-dihydro-7H-pyrano[2,3-g]indazol-1-yl)-1-methylethylamine]. *Pharmacol Biochem Behav*. 2009; 91:307–314. [PubMed: 18718483]
47. May JA, Sharif NA, McLaughlin MA, Chen HH, Severns BS, Kelly CR, Holt WF, Young R, Glennon RA, Hellberg MR, Dean TR. Ocular hypotensive response in nonhuman primates of (8*R*)-1-[(2*S*)-2-aminopropyl]-8,9-dihydro-7H-pyrano[2,3-g]indazol-8-ol, a selective 5-HT₂ receptor agonist. *J Med Chem*. 2015; 58:8818–8833. [PubMed: 26551970]
48. Glennon RA, Young R. Further investigation of the discriminative stimulus properties of MDA. *Pharmacol Biochem Behav*. 1984; 20:501–505. [PubMed: 6728867]
49. Glennon RA, Young R. MDA: An agent that produces stimulus effects similar to those of 3,4-DMA, LSD and cocaine. *Eur J Pharmacol*. 1984; 99:249–250. [PubMed: 6145599]
50. Young R, Glennon RA. A three-lever operant procedure differentiates the stimulus effects of R(-)-MDA from S(+)-MDA. *J Pharmacol Exp Ther*. 1996; 276:594–601. [PubMed: 8632326]
51. Kamilar-Britt P, Bedi G. The prosocial effects of 3,4-methylenedioxymethamphetamine (MDMA): Controlled studies in humans and laboratory animals. *Neurosci Biobehav Rev*. 2015; 57:433–446. [PubMed: 26408071]
52. Lyon RA, Glennon RA, Titeler M. 3,4-Methylenedioxymethamphetamine (MDMA): Stereoselective interactions at brain 5-HT₁ and 5-HT₂ receptors. *Psychopharmacology (Berl)*. 1986; 88:525–526. [PubMed: 2871581]
53. Nichols DE, Oberlender R. Structure-activity relationships of MDMA-like substances. *NIDA Res Monogr*. 1989; 94:1–29.
54. Glennon RA. Stimulus properties of hallucinogenic phenylalkylamines and related designer drugs: Formulation of structure-activity relationships. *NIDA Res Monogr*. 1989; 94:43–67. [PubMed: 2575229]
55. Bondareva T, Wesolowska A, Dukat M, Lee M, Young R, Glennon RA. *S*(+)- and *R*(-)-*N*-Methyl-1-(3,4-methylenedioxyphenyl)-2-aminopropane (MDMA) as discriminative stimuli: Effect of cocaine. *Pharmacol Biochem Behav*. 2005; 82:531–538. [PubMed: 16337676]
56. Broadbent J, Michael EK, Appel JB. Generalization of cocaine to the isomers of 3,4-methylenedioxymphetamine and 3,4-methylenedioxymethamphetamine: Effects of training dose. *Drug Develop Res*. 1989; 16:443–450.
57. Baker LE, Broadbent J, Michael EK, Matthews PK, Metosh CA, Saunders RB, West WB, Appel JB. Assessment of the discriminative stimulus effects of the optical isomers of ecstasy (3,4-methylenedioxy-methamphetamine; MDMA). *Behav Pharmacol*. 1995; 6:263–275. [PubMed: 11224335]

58. Young R, Glennon RA. MDMA (N-methyl-3,4-methylenedioxyamphetamine) and Its stereoisomers: Similarities and differences in behavioral effects in an automated activity apparatus in mice. *Pharmacol Biochem Behav.* 2008; 88:318–331. [PubMed: 17904622]
59. Setola V, Hufeisen SJ, Grande-Allen KJ, Vesely I, Glennon RA, Blough B, Rothman RB, Roth BL. 3,4-Methylenedioxymethamphetamine (MDMA, "Ecstasy") induces fenfluramine-like proliferative actions on human cardiac valvular interstitial cells in vitro. *Mol Pharmacol.* 2003; 63:1223–1229. [PubMed: 12761331]
60. Rothman RB, Baumann MH. Therapeutic potential of monoamine transporter substrates. *Curr Topics Med Chem.* 2006; 6:1845–1859.
61. Rothman RB, Baumann MH. Balance between dopamine and serotonin release modulates behavioral effects of amphetamine-type drugs. *Ann NY Acad Sci.* 2006; 1074:245–260. [PubMed: 17105921]
62. Young R, Bondarev M, Glennon RA. An examination of isomeric phenylpropanolamines in (-)-ephedrine-trained rats. *Drug Alcohol Depend.* 1999; 57:1–6. [PubMed: 10617308]
63. Bondareva TS, Young R, Glennon RA. Central stimulants as discriminative stimuli. Asymmetric generalization between (-)-ephedrine and S(+)-methamphetamine. *Pharmacol Biochem Behav.* 2002; 74:157–162. [PubMed: 12376163]
64. Rothman RB, Vu N, Partilla JS, Roth BL, Hufeisen SJ, Compton-Toth BA, Birkes J, Young R, Glennon RA. In vitro characterization of ephedrine-related stereoisomers at biogenic amine transporters and the receptorome reveals selective actions as norepinephrine transporter substrates. *J Pharmacol Exp Ther.* 2003; 307:138–145. [PubMed: 12954796]
65. Dulloo AG, Seydoux J, Girardier L. Potentiation of the thermogenic antiobesity effects of ephedrine by dietary methylxanthines: Adenosine antagonism or phosphodiesterase inhibition? *Metabolism.* 1992; 41:1233–1241. [PubMed: 1435297]
66. Young R, Gabryszuk M, Glennon RA. (-)-Ephedrine caffeine mutually potentiate one another's amphetamine-like stimulus effects. *Pharmacol Biochem Behav.* 1998; 61:169–173. [PubMed: 9738532]
67. Holloway FA, Michaelis RC, Huerta PL. Caffeine-phenylethylamine combinations mimic the amphetamine discriminative cue. *Life Sci.* 1985; 36:723–730. [PubMed: 3974408]
68. Gauvin DV, Harland RD, Michaelis RC, Holloway FA. Caffeine-phenylethylamine combinations mimic the cocaine discriminative cue. *Life Sci.* 1989; 44:67–73. [PubMed: 2913437]
69. Harland RD, Gauvin DV, Michaelis RC, Carney JM, Seale TW, Holloway FA. Behavioral interaction between cocaine and caffeine: A drug discrimination analysis in rats. *Pharmacol Biochem Behav.* 1989; 32:1017–1023. [PubMed: 2798526]
70. Reid D, Goudie AJ. Discriminative stimulus properties of β -phenylethylamine, deuterated β -phenylethylamine, phenylethanolamine and some metabolites of phenylethylamine in rodents. *Pharmacol Biochem Behav.* 1986; 24:1547–1553. [PubMed: 3737623]
71. PEA Forum website. <https://drugs-forum.com/forum/showthread.php?t=60910>
72. Ziegler G, Stojacic E, Stumpf B. Vorkommen von beta-phenylethylamin und seinen Derivaten in Kakao und Kakaoerzeugnissen. *Z Lebensm Unters Forsch.* 1992; 195:235–238. [PubMed: 1413998]
73. Glennon RA, Young R. (+)Amphetamine-stimulus generalization to an herbal ephedrine product. *Pharmacol Biochem Behav.* 2000; 65:655–658. [PubMed: 10764918]
74. Glennon RA. Bath salts, mephedrone, and methylenedioxypyrovalerone as emerging illicit drugs that will need targeted therapeutic intervention. *Adv Pharmacol.* 2014; 69:581–620. [PubMed: 24484988]
75. Glennon, RA., Dukat, M. Structure-activity relationships of synthetic cathinones. In: Baumann, MH, Glennon, RA., Wiley, J., editors. *New Psychoactive Substances*. Springer; in press
76. Glennon RA, Showalter D. The effect of cathinone and several related derivatives on locomotor activity. *Res Commun Subst Abuse.* 1981; 2:186–192.
77. Glennon RA. Discriminative Stimulus Properties of Phenylisopropylamine Derivatives. *Drug Alcohol Depend.* 1986; 17:119–134. [PubMed: 2874967]
78. Glennon RA, Yousif M, Naiman N, Kalix P. Methcathinone: A new and potent amphetamine-like agent. *Pharmacol Biochem Behav.* 1987; 26:547–551. [PubMed: 3575369]

79. Young R, Glennon RA. Discriminative stimulus effects of S(-)-methcathinone (MCAT): A potent stimulant drug of abuse. *Psychopharmacology*. 1998; 140:250–256. [PubMed: 9877004]
80. Iversen LE. Consideration of the cathinones. Advisory Council on the Misuse of Drugs. A report submitted to the Home Secretary of the UK. Mar 31.2010
81. Sakloth F, Kolanos R, Mosier PD, Bonano JS, Banks ML, Partilla JS, Baumann MH, Negus SS, Glennon RA. Steric parameters, molecular modeling and hydrophobic interaction analysis of the pharmacology of para-substituted methcathinone analogues. *Br J Pharmacol*. 2015; 172:2210–2218. [PubMed: 25522019]
82. Kolanos R, Solis E, Sakloth F, De Felice LJ, Glennon RA. Deconstruction" of the abused synthetic cathinone methylenedioxypyrovalerone (MDPV) and an examination of effects at the human dopamine transporter. *ACS Chem Neurosci*. 2013; 4:1524–1529. [PubMed: 24116392]
83. Glennon RA, Young R. Neurobiology of 3,4-methylenedioxypyrovalerone (MDPV) and α -pyrrolidinovalerophenone (α -PVP). *Brain Res Bull*. 2016; 126:111–126. [PubMed: 27142261]
84. Kolanos R, Sakloth F, Jain AD, Partilla JS, Baumann MH, Glennon RA. Structural modification of the designer stimulant α -pyrrolidinovalerophenone (α -PVP) influences potency at dopamine transporters. *ACS Chem Neurosci*. 2015; 6:1726–1731. [PubMed: 26217965]
85. Kolanos R, Partilla JS, Baumann MH, Hutsell BA, Banks ML, Negus SS, Glennon RA. Stereoselective actions of methylenedioxypyrovalerone (MDPV) to inhibit dopamine and norepinephrine transporters and facilitate intracranial self-stimulation in rats. *ACS Chem Neurosci*. 2015; 6:771–777. [PubMed: 25688761]
86. Young R, Glennon RA. The stimulus effect of 5,6,7,8-tetrahydro-1,3-dioxolo[4,5-g]isoquinoline is similar to that of cocaine but different from that of amphetamine. *Pharmacol Biochem Behav*. 2002; 71:205–213. [PubMed: 11812524]
87. Glennon RA, Young R, Rangisetty JB. Further characterization of the stimulus properties of 5,6,7,8-tetrahydro-1,3-dioxolo[4,5-g]isoquinoline. *Pharmacol Biochem Behav*. 2002; 72:379–387. [PubMed: 11900809]
88. Young R, Batkai S, Dukat M, Glennon RA. TDIQ (5,6,7,8-tetrahydro-1,3-dioxolo[4,5-g]isoquinoline) exhibits anxiolytic-like activity in a marble-burying assay in mice. *Pharmacol Biochem Behav*. 2006; 84:62–73. [PubMed: 16750844]
89. Glennon RA. Discriminative stimulus properties of the 5-HT_{1A} agonist 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH DPAT). *Pharmacol Biochem Behav*. 1986; 25:135–139. [PubMed: 2944129]
90. Björk L, Höök BB, Nelson DL, Andén NE, Hacksell U. Resolved N,N-dialkylated 2-amino-8-hydroxytetralins: Stereoselective interactions with 5-HT_{1A} receptors in the brain. *J Med Chem*. 1989; 32:779–783. [PubMed: 2522991]
91. Naiman N, Lyon RA, Bullock AE, Rydelek LT, Titeler M, Glennon RA. 2-(Alkylamino)tetralin derivatives: interaction with 5-HT_{1A} serotonin binding sites. *J Med Chem*. 1989; 32:253–256. [PubMed: 2521252]
92. Ariens, EJ. Agonists and antagonists – Their structural relationship. In: Ariens, EJ., editor. *Drug Design*. Vol. I. Academic Press; NY: 1971. p. 162-193.
93. Hauck, AE. Doctoral dissertation. Virginia Commonwealth University; Richmond, Virginia: May. 1985 CNS stimulants and serotonergic properties of phenylalkylamines.
94. Glennon RA, Young R. MDMA stimulus generalization to the 5-HT_{1A} serotonin agonist 8-hydroxy-2-(di-*n*-propylamino)tetralin. *Pharmacol Biochem Behav*. 2000; 66:483–488. [PubMed: 10899359]
95. Khorana N, Young R, Glennon RA. Effect of 8-hydroxy-2-(N,N-di-*n*-propylamino)tetralin and MDMA on the discriminative stimulus effects of the classical hallucinogen DOM in rats. *Pharmacol Biochem Behav*. 2009; 91:385–392. [PubMed: 18778728]
96. Walker, JM., Martin, WJ., Hohmann, AG., Hemstreet, MK., Roth, JS., Leitner, ML., Weiser, SD., Patrick, SL., Patrick, RL., Matsumoto, RR. Role of sigma receptors in brain mechanisms of movement. In: Itzhak, Y., editor. *Sigma Receptors*. 1994. p. 205-224.
97. Liu, Y., Yu, Y., Shaikh, J., Pouw, B., Daniels, A., Chen, Q-D., Matsumoto, RR. σ receptors and drug abuse. In: Matsumoto, RR. Bowen, WD., Su, T-P., editors. *Sigma Receptors, Chemistry, Cell Biology and Clinical Implications*. Springer; 2007. p. 315-336.

98. Ablordeppey, SY., Glennon, RA. Pharmacophore models for sigma1 receptor binding. In: Matsumoto, RR. Bowen, WD., Su, T-P., editors. *Sigma Receptors, Chemistry, Cell Biology and Clinical Implications*. Springer; 2007. p. 71-08.
99. Glennon RA. Pharmacophore identification for sigma-1 (σ_1) receptor binding: Application of the "Deconstruction-Reconstruction-Elaboration" approach. *Mini-Rev Med Chem*. 2005; 5:927–940. [PubMed: 16250835]
100. Glennon RA, Young R, Herndon JL. Antagonism of a (+)N-allylnormetazocine stimulus by (-)PPAP and several structurally related analogs. *Pharmacol Biochem Behav*. 1993; 45:865–869. [PubMed: 8105490]
101. Ablordeppey SY, Fischer JB, Law H, Glennon RA. Probing the proposed phenyl-A region of the sigma-1 receptor. *Bioorg Med Chem*. 2002; 10:2759–2765. [PubMed: 12057665]
102. a) Glennon RA. Binding characteristics of σ_2 receptor ligands. *Brazil J Pharm Sci*. 2005; 41:1–12. b) Abate C, Mosier P, Berardi F, Glennon RA. A structure-affinity and comparative molecular field analysis of sigma-2 (σ_2) receptor ligands. *CNS Agents Med Chem*. 2009; 9:246–257.
103. Glennon RA, Siripurapu U, Roth BL, Kolanos R, Bondarev ML, Sikazwe D, Lee M, Dukat M. The medicinal chemistry of 5-HT₆ receptor ligands with a focus on arylsulfonyletryptamine analogs. *Curr Top Med Chem*. 2010; 10:579–595. [PubMed: 20166945]
104. Frantz KJ, Hansson DG, Stouffer LH, Parsons A. 5-HT₆ receptor antagonism potentiates the behavioral and neurochemical effects of amphetamine but not cocaine. *Neuropharmacology*. 2002; 42:170–180. [PubMed: 11804613]
105. Pullagurla M, Bondareva T, Young R, Glennon RA. Modulation of the stimulus effects of (+)amphetamine by the 5-HT₆ antagonist MS-245. *Pharmacol Biochem Behav*. 2004; 78:263–268. [PubMed: 15219766]
106. Young R, Bondareva T, Wesolowska A, Young S, Glennon RA. Effect of the 5-HT₆ serotonin antagonist MS-245 on the actions of (-)nicotine. *Pharmacol Biochem Behav*. 2006; 85:170–177. [PubMed: 16950502]
107. Glennon RA, Young R, Jacyno JM. Indolealkylamine and phenalkylamine hallucinogens: Effect of α -methyl and N-methyl substituents on behavioral activity. *Biochem Pharmacol*. 1983; 32:1267–1273. [PubMed: 6573879]
108. Lyon RA, Titeler M, Seggel MR, Glennon RA. Indolealkylamine analogs share 5-HT₂ binding characteristics with phenalkylamine hallucinogens. *Eur J Pharmacol*. 1988; 145:291–297. [PubMed: 3350047]
109. Glennon, RA. Discriminative stimulus properties of site-selective serotonin agonists. In: Colpaert, FC., Balster, RL., editors. *Transduction Mechanisms of Drug Stimuli*. Springer Verlag; Berlin: 1988. p. 15-31.
110. Hong SS, Young R, Glennon RA. Discriminative stimulus properties of α -ethyltryptamine optical isomers. *Pharmacol Biochem Behav*. 2001; 70:311–316. [PubMed: 11701202]
111. Glennon RA, Misenheimer BR. Stimulus effects of N-monoethyl-1-(3,4-methylenedioxyphenyl)-2-aminopropane (MDE) and N-hydroxy-1-(3,4-methylenedioxyphenyl)-2-aminopropane (N-OH MDA) in rats trained to discriminate MDMA from saline. *Pharmacol Biochem Behav*. 1989; 33:909–912. [PubMed: 2575759]
112. Glennon RA. MDMA-Like stimulus effects of α -ethyltryptamine and the α -ethyl homolog of DOM. *Pharmacol Biochem Behav*. 1993; 46:459–462. [PubMed: 7903460]
113. Glennon RA, Bondareva T, Young R. α -Ethyltryptamine (α -ET) as a discriminative stimulus in rats. *Pharmacol Biochem Behav*. 2006; 85:448–453. [PubMed: 17112572]
114. Blough BE, Landavazo A, Partilla JS, Decker AM, Page KM, Baumann MH, Rothman RB. Alpha-ethyltryptamines as dual dopamine-serotonin releasers. *Bioorg Med Chem Lett*. 2014; 24:4754–4758. [PubMed: 25193229]
115. Rothman RB, Baumann MH, Savage JE, Rauser L, McBride A, Hufeisen SJ, Roth BL. Evidence for possible involvement of 5-HT_{2B} receptors in the cardiac valvulopathy associated with fenfluramine and other serotonergic medications. *Circulation*. 2000; 102:2836–2841. [PubMed: 11104741]

Biography

Dr. Glennon is Professor, Department Chairman, and the *Alfred and Frances Burger Distinguished Professor of Medicinal Chemistry* at Virginia Commonwealth University. He has had a long-standing interest in the medicinal chemistry, mechanisms of action, and behavioral pharmacology of neuropsychiatric agents and selected drugs of abuse, and has published >450 papers and book chapters in these areas. Some of his achievements include the American Pharmaceutical Association's *Research Achievement Award*, the European Federation of Medicinal Chemistry's *Order of the Oak and Tulip Medal*, and induction into the ACS Medicinal Chemistry Division's *Hall of Fame*.

Figure 1.
The “*phenylalkylaminegnome*”.

Figure 2.

Examples of a few common agents containing an embedded phenylethyl-amine (1) moiety: lysergic acid diethylamide (2), morphine (3), venlafaxine (4), ziprasidone (5), lorcaserin (6), and the 5-HT_{1A} serotonin receptor agonist 8-hydroxy-2-(di-*n*-propylamino)tetalin (7).

Figure 3.

Structural relationships among several psychoactive arylalkylamines: the central stimulant amphetamine (**8**), and the classical hallucinogens mescaline (**9**), 5-methoxy-*N,N*-dimethyltryptamine (5-OMe DMT; **10**), 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (DOM; **11**) and its halogenated counterparts DOB (**12**) and DOI (**13**).

Figure 4.

A typical dose-response plot for stimulus generalization studies. Animals trained to discriminate 1.0 mg/kg of a hypothetical training drug (solid squares) from saline vehicle make >80% of their responses on the drug-appropriate lever following administration of this dose, and <20 of their responses on this lever when administered vehicle (data not shown). Lower doses of the training drug result in decreased drug-appropriate responding (solid squares) such that an ED_{50} value can be calculated. When doses of challenge drugs *A* and *B* (open squares and open circles) are administered, stimulus generalization is said to have occurred if the animals produce >80% training-drug-appropriate responding at some dose. Here, drugs *A* and *B* substituted – implying a similarity of stimulus effects, and ED_{50} doses can be calculated. Drug *C* (open triangles) produced vehicle-appropriate (i.e. <20 drug-appropriate) responding at the highest doses examined. Some agents produce >20% but <80% drug-appropriate responding at the highest dose(s) examined; this is termed partial generalization.

Figure 5. Stimulus generalization. A challenge drug might or might not substitute for (i.e., the challenge drug might or might not be recognized by) the trained animals. Stimulus generalization suggests a similarity of stimulus effects.

Figure 6. Stimulus antagonism. Animals trained to a specific drug will respond on the “vehicle appropriate” lever if a combination of the training drug and the antagonist result in stimulus antagonism.

Figure 7.
Examples of phenylalkylamine-derived 5-HT_{2A} receptor antagonists.

Figure 8. 5-HT₂ receptor agonists **26**, **27**, **29–31**, **40**, **41**, and the 5-HT₂ receptor antagonist M100907 (**28**).

Figure 9.

Structures of several MDA (**42**)-related compounds: MDMA (**43**), PMA (**44**), PMMA (**45**), 3,4-DMA (**46**), and MMA (**47**).

Figure 10.

The stimulus properties of numerous arylalkylamines (indolealkylamines and phenylalkylamines) have been classified as being primarily of three types: DOM-like, amphetamine (AMPH)-like, or PMMA-like (reviewed¹⁸). Certain agents produce a combination of effects; for example, MDMA shares stimulus properties with amphetamine and PMMA and is best characterized as producing an A/P-like effect. (±)MDA produces all three stimulus effects and best associated with the common intersect.

Figure 11.

Structures of *S*(+)-amphetamine [*S*(+)-AMPH], *S*(+)-methamphetamine [*S*(+)-METH], and their phenylpropanolamine counterparts.

Figure 12.

Chemical structures of cathinone (originally termed β -ketoamphetamine), its optical isomers, and methcathinone.

Figure 13.
Examples of synthetic cathinones.

Figure 14.
Conformationally-constrained phenylalkylamines.

Figure 15.
Chemical structures of diazepam (**69**), buspirone (**70**), and NAN-190 (**71**).

Figure 16.
8-OH DPAT (7)-related analogs.

Figure 17.
Examples of arylalkylamines examined at σ_1 receptors.

Figure 18.
5-HT₆ receptor ligands developed in our laboratory.

Figure 19.

Figure 18. Chemical structures of indolealkylamines α-MeT (**101**) and α-ET (**102**), and the 5-HT releasing agent fenfluramine (**103**).

h5-HT_{2A} receptor binding data for a few representative examples of phenylalkylamines using [³H]ketanserin (³H]KET),³⁷ [³H]DOB³⁸ or [¹²⁵I]DOI²⁷ as radioligand. See references for additional binding data.

Table 1

	X	R ₁	R ₂	K _i , nM		
				[³ H]KET	[³ H]DOB	[¹²⁵ I]DOI
14	H	H	H	5,200	268	211
15	OCH ₃	H	H	1,200	81	57.9
12	Br	H	H	41	0.8	0.6
16	Br	CH ₃	CH ₃	380	-	94.2
17	Br	C ₃ H ₇	H	-	-	88.5
13	I	H	H	19	0.7	0.7

5-HT_{2A} receptor binding data for selected phenylethylamines using [³H]-ketanserin as radioligand.⁴¹

Table 2

	R	R ₂	R ₅	X	K _i , nM
1	H	H	H	H	>10,000
8	CH ₃	H	H	H	>10,000
18	CH ₃	OCH ₃	H	H	>10,000
19	CH ₃	H	OCH ₃	H	>10,000
20	H	OCH ₃	OCH ₃	H	2,820
14	CH ₃	OCH ₃	OCH ₃	H	4,720
12	CH ₃	OCH ₃	OCH ₃	Br	32
21	CH ₃	OCH ₃	OCH ₃	(CH ₂) ₃ -Ph	30
22	CH ₃	OCH ₃	H	(CH ₂) ₃ -Ph	8
23	CH ₃	H	OCH ₃	(CH ₂) ₃ -Ph	17

Table 35-HT_{2A} serotonin receptor affinity of β -methoxy and hydroxyl DOB analogs.⁴⁵

	R	Stereochemistry		5-HT _{2A} <i>K_i</i> , nM
		α	β	
32	-OCH ₃	<i>R</i>	<i>S</i>	17.4
33	-OCH ₃	<i>S</i>	<i>R</i>	0.8
34	-OCH ₃	<i>S</i>	<i>S</i>	6.0
35	-OCH ₃	<i>R</i>	<i>R</i>	0.3
36	-OH	<i>R</i>	<i>S</i>	9.2
37	-OH	<i>S</i>	<i>R</i>	1.1
38	-OH	<i>S</i>	<i>S</i>	10.0
39	-OH	<i>R</i>	<i>R</i>	0.5
12 (DOB)	-H	<i>R</i>	--	0.2

Results of stimulus generalization studies using rats trained to discriminate either MDMA (1.5 mg/kg) or PMMA (1.25 mg/kg) from saline vehicle in a 2-lever procedure.

Table 4

		ED ₅₀ (mg/kg) ^a

	S(+)-46	R(-)-46	S(+)-44	R(-)-44	R(-)-47
MDMA-trained	6.1	5.4	PG	S	1.4
PMMA-trained	2.6	3.0	PG	PG	PG

^aWhere stimulus generalization (i.e., >80% training-drug appropriate responding occur- red), an ED₅₀ value is provided. S = saline-like responding; no generalization (i.e., <20% drug-appropriate responding). PG = partial generalization (>20% but <80% drug-appropriate responding. PG cannot be reliably interpreted; it simply indicates differences in the stimulus effects of two agents.

Table 5

Action of MDMA (**43**), MDA (**42**), and PMMA (**45**) as releasing agents at the serotonin (SERT), dopamine (DAT) and norepinephrine (NET) transporters.^{18,59,60}

Agent	EC ₅₀ , nM ^a		
	SERT	DAT	NET
(±)MDMA (43)	72	278	110
<i>S</i> (+)MDMA	74	142	136
<i>R</i> (-)MDMA	340	3,700	560
(±)MDA (42)	160	190	108
<i>S</i> (+)MDA	100	98	50
<i>R</i> (-)MDA	310	900	290
<i>S</i> (+)PMMA	41	1,000	147
<i>R</i> (-)PMMA	134	1,600	>14,000
<i>S</i> (+)Amphetamine	1,765	25	7

^aData, although from different publications, were obtained from the same laboratory.

Table 6

A comparison of stimulus generalization potencies of selected agents in rats trained to discriminate *S*(+)amphetamine (AMPH), *S*(+)methamphetamine (METH), or *S*(-)methcathinone (MCAT) from saline vehicle.⁶³

Training Drug:	ED ₅₀ , mg/kg		
	<i>S</i> (+)AMPH ^a	<i>S</i> (+)METH ^a	<i>S</i> (-)MCAT ^a
Test Agent			
<i>S</i> (+)Amphetamine	0.44	0.28	0.23
<i>S</i> (-)Cathinone	0.34	_b	0.17
<i>S</i> (+)Methamphetamine	0.20	0.06	0.17
<i>S</i> (-)Methcathinone	0.18	0.21	0.11
Cocaine	5.63	6.68	1.47

^a Training doses were 1.0, 1.0, and 0.5 mg/kg for *S*(+)AMPH, *S*(+)METH, and *S*(-)MCAT, respectively.

^b Not evaluated.

Table 7

5-HT_{1A} receptor affinities of several 8-methoxyaminotetralin analogs.⁹¹

	R	R'	5-HT _{1A} K _i nM ^a
75	-CH ₂ CH ₂ CH ₃	-CH ₂ CH ₂ CH ₃	1.3
76	-H	-H	53
77	-CH ₃	-CH ₂ CH ₂ CH ₃	2.1
78	-H	-CH ₂ CH ₂ CH ₃	2.3
79	-CH ₃	-(CH ₂) ₃ -Ph	2.0
80	-H	-(CH ₂) ₃ -Ph	2.5
81	-H	-(CH ₂) ₄ -Ph	5.6

^aFor comparison, the K_i for 8-OH DPAT (7) = 1.2 nM.

Representative results of stimulus generalization studies using rats trained to discriminate either DOM, (+)amphetamine (AMPH), MDMA, PMMA, or (±)α-ET from vehicle.^{109–113}

Table 8

Training Drug:	ED ₅₀ , mg/kg ^a			
	DOM	AMPH	MDMA	PMMA
Test Agent				(±)α-ET
(±)α-ET (102)	6.6	PG	3.5	_b 1.3
R(-)α-ET	PG ^c	7.8	1.3	1.6
S(+)-α-ET	2.7	PG ^d	2.0	1.4 1.3
PMMA (45)	S	S	0.2	0.4 0.7
(+)Amphetamine (8)	S	0.4	PG	S PG
DOM (11)	0.4	S	S	S 0.4

^a Here stimulus generalization failed to occur: S = vehicle-appropriate responding, and PG = partial generalization (i.e., >20% but <80% drug-appropriate responding).

^b Not evaluated.

^c 33% DOM-appropriate responding.

^d 53% AMPH-appropriate responding.