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5-HT_{2A} SEROTONIN RECEPTOR BIOLOGY: Interacting proteins, kinases and paradoxical regulation

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Abstract

5-hydroxytryptamine_{2A} (5-HT_{2A}) serotonin receptors are important pharmacological targets for a large number of central nervous system and peripheral serotonergic medications. In this review article I summarize work mainly from my lab regarding serotonin receptor anatomy, pharmacology, signaling and regulation. I highlight the role of serotonin receptor interacting proteins and the emerging paradigm of G-protein coupled receptor functional selectivity.

Keywords

PDZ domain; functional selectivity; antipsychotic; psychoactive; RSK2; caveolin

1.0 INTRODUCTION

Serotonin (5-hydroxytryptamine; 5-HT) is a neurotransmitter and factor released by platelets which is responsible for regulating a large number of peripheral physiological processes including platelet aggregation, vascular and non-vascular smooth muscle contraction and relaxation, mitogenesis, urogenital function, gastrointestinal motility and cardiovascular function (Berger et al., 2009). In the central nervous system (CNS), 5-HT exerts a modulatory influence on essentially every major CNS function including memory, cognition, emotion, perception, mood and consciousness (Allen et al., 2008a; Berger et al., 2009). To mediate this large number of functions, at least 15 distinct 5-HT receptors have evolved in humans which are divided into 7 main families (5-HT₁, 5-HT₂, 5-HT₃, 5-HT₄, 5-HT₅, 5-HT₆, 5-HT₇) each of which can have several members (e.g. 5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C}) (Hoyer et al., 1994). With the exception of the 5-HT₃ serotonin receptors, which are cation channels (Maricq et al., 1991), serotonin receptors are members of the G-protein coupled receptor superfamily (Kroeze and Roth, 1998; Kroeze et al., 2002; Kroeze et al., 2003). The 5-HT₂-family serotonin receptors (Roth et al., 1998), have emerged as important potential therapeutic targets for antipsychotic, antidepressant, anorectic, anti-insomnia, cardiovascular and anxiolytic medications (Kozikowski et al.,; Roth et al., 2004; Roth, 2007; Berger et al., 2009; Cho et al., 2009). This particular review will focus on 5-HT_{2A} serotonin receptors.

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2.0. 5-HT_{2A} receptors

2.1 Anatomy and Pharmacology

5-HT_{2A} serotonin receptors are among the most widely studied 5-HT receptors and had been known in the pre-molecular cloning era as the “D” (Gaddum and Picarelli, 1957) “S2” (Leysen et al., 1978) or “5-HT2” (Peroutka and Snyder, 1979) serotonin receptor see (Leysen, 2004) for recent historical review. Although it was known that [³H]-spiperone (Leysen et al., 1978) and [³H]-LSD (Peroutka and Snyder, 1979) could be used to label a ‘5-HT2’-like receptor, the relative non-selectivity of these radioligands made their routine use difficult. The discovery of [³H]-ketanserin as a reasonably selective ligand for 5-HT_{2A} receptors (Leysen et al., 1982) was thus a major advance and greatly potentiated investigation of these important receptors. [³H]-ketanserin is not without its drawbacks, having relatively high affinity for α₁-adrenergic receptors (Leysen et al., 1982) and tetrabenazine-sensitive vesicular monoamine transporters in stratum (Leysen et al., 1987; Roth et al., 1987) and moderate affinity for 5-HT_{2C} receptors (Choudhary et al., 1992). Several 5-HT_{2A}-selective (or preferring) ligands have been subsequently developed of which the most useful are M100907 (formerly known as MDL 100,907) (Kehne et al., 1996) and MDL 11,939 (Pehek et al., 2006). Of these M100907 (Potkin et al., 2001), SR46349B (Meltzer et al., 2004) and pimavanserin (Meltzer et al.,; Abbas and Roth, 2008b) have shown at least some efficacy in clinical trials for a variety of conditions including insomnia, psychosis and schizophrenia (Abbas and Roth, 2008b).

The 5-HT_{2A} receptor also represents the main molecular target for lysergic acid diethylamide (LSD) and LSD-like hallucinogens (Glennon et al., 1984) (Titeler et al., 1988). Prior to the cloning of the 5-HT_{2A} receptor, there was controversy as to whether LSD and related hallucinogens were agonists (Seggal et al., 1987) or antagonists (Pierce and Peroutka, 1990) at 5-HT_{2A} receptors. It had also been proposed that there was a distinct subtype of 5-HT₂-receptors which was selective for phenylisopropylamines (Pierce and Peroutka, 1989). This controversy was settled with the demonstration that the cloned 5-HT_{2A} receptor bound both phenylisopropylamines as well as classical antagonists (Teitler et al., 1990). Most now accept the hypothesis that the 5-HT_{2A} receptor is the main site of action of LSD-like hallucinogens (Nichols, 2004).

The rat 5-HT_{2A} receptor was cloned in 1988 by the late Dolan Pritchett and colleagues (Pritchett et al., 1988) with the human 5-HT_{2A} receptor reported in 1990 by David Julius and colleagues (Julius et al., 1990). The rodent and human 5-HT_{2A} receptors have similar, but not identical, amino acid sequences (Julius et al., 1990; Roth et al., 1998; Kroeze et al., 2002; Kroeze et al., 2003) leading to some pronounced differences in the pharmacology of N-1 substituted tryptamines and ergolines (Johnson et al., 1994; Johnson et al., 1995).

Quantitative receptor autoradiography studies have reproducibly demonstrated that 5-HT_{2A} receptors are most highly expressed in deep layers of the human and rodent cerebral cortex—particularly Layer V and its subdivisions (Pazos et al., 1985; Pazos et al., 1987; Roth et al., 1987). Additionally, 5-HT_{2A} receptors are highly expressed in rodent olfactory tubercle (Pazos et al., 1985) with moderate-to-low expression levels in other brain regions including hippocampus, amygdala, nucleus accumbens, striatum and hypothalamus (Pazos et al., 1985; Pazos et al., 1987). In general, *in situ* hybridization studies have verified the distribution of 5-HT_{2A} receptors (Pompeiano et al., 1994).

Immunohistochemical studies of 5-HT_{2A} receptors have been hampered by the lack of reliable antibodies (Xia et al., 2003b) although many studies have demonstrated that 5-HT_{2A} receptors are highly enriched in Layer V pyramidal neurons (Willins et al., 1997; Jakab and Goldman-Rakic, 1998) (Hamada et al., 1998; Cornea-Hebert et al., 1999)—particularly in the

somato-dendritic compartment in rats (Willins et al., 1997; Miner et al., 2003) and mice (Xia et al., 2003b) (Abbas et al., 2009). Immunohistochemical studies have also found 5-HT_{2A} receptors to be expressed to a lesser extent in parvalbumin-expressing GABA-ergic interneurons (Willins et al., 1997) (Magalhaes et al.,; Weber and Andrade). More recent studies using validated and apparently reliable commercial antibodies have appeared (developed in a manner identical to those originally described by my group (Roth et al., 1995; Berry et al., 1996)). These studies have verified our initial findings that 5-HT_{2A} receptors are most highly enriched in mouse Layer V pyramidal neurons in the somatodendritic compartment (Magalhaes et al.,; Weber and Andrade) and to a lesser extent in mouse parvalbumin-containing interneurons (Weber and Andrade) in confirmation of our initial studies in the rat (Willins et al., 1997).

2.2 Signal transduction

In 1984, three groups independently discovered that 5-HT_{2A} receptors signal via activation of a phosphoinositide-specific phospholipase C in vascular smooth muscle (Roth et al., 1984), brain (Conn and Sanders-Bush, 1984) and platelets (Leysen et al., 1984). We subsequently discovered that signaling was subject to feed-back regulation by protein kinase C (Roth et al., 1986) and that signaling can also be via ion channel activation (Nakaki et al., 1985). Subsequent studies by many labs have validated and extended these findings (see (Raymond et al., 2001) for review). Since then, 5-HT_{2A} receptors have been demonstrated modulate arachidonic acid release (Felder et al., 1990), cAMP production (Berg et al., 1994), Arf-1 (Robertson et al., 2003), various immediate early genes (Nichols and Sanders-Bush, 2002; Nichols et al., 2003; Nichols and Sanders-Bush, 2004), nitric oxide production (Miller et al., 1997) and other signaling pathways (Raymond et al., 2001).

2.3 Interacting proteins

The 5-HT₂-family receptors have canonical Type I PDZ-binding motifs (PDZ= Post synaptic density protein (PSD95), *Drosophila* disc large tumor suppressor (DlgA), and Zonula occludens-1 protein (zo-1)). Not surprisingly, a large number of PDZ-domain proteins have been identified which interact with 5-HT_{2A} receptors including, most prominently, MUPP-1 (*Multi-PDZ Protein 1*) (Becamel et al., 2001) (Jones et al., 2009) and PSD-95 (*Post-Synaptic Density protein-95*) (Xia et al., 2003a; Xia et al., 2003b; Becamel et al., 2004; Gavarini et al., 2004; Abbas et al., 2009). My lab has been particularly interested in the interaction of 5-HT_{2A} receptors with PSD-95 as this interaction appears essential for the somatodendritic targeting of 5-HT_{2A} receptors *in vitro* (Xia et al., 2003a; Xia et al., 2003b) and *in vivo* (Abbas et al., 2009). Additionally, disruption 5-HT_{2A}-PSD-95 interactions has been demonstrated to reduce hyperalgesia in a neuropathic pain model and to enhance the effectiveness of serotonin-selective reuptake inhibitors in ameliorating this pain.

5-HT_{2A} receptors also have functionally important interactions with the serine-threonine kinase RSK2 (*Ribosomal S6 Kinase-2*) (Sheffler et al., 2006; Strachan et al., 2009a; Strachan et al., 2009b). RSK2 apparently acts as a GPCR-kinase which induces a 'tonic-brake' in signaling directly phosphorylating 5-HT_{2A} receptors in the i3 loop (Strachan et al.,; Sheffler et al., 2006; Strachan et al., 2009a; Strachan et al., 2009b) (Fig 1). Given that RSK2 is deleted in a psychosis-mental retardation condition called Coffin-Lowry Syndrome (Hanauer and Young, 2002) and that genetic deletion of RSK2 leads to an augmentation of 5-HT_{2A} signaling (Sheffler et al., 2006; Strachan et al., 2008; Strachan et al., 2009a), our findings imply that augmented 5-HT_{2A} signaling might play a role in psychosis susceptibility as recently suggested by Lambe and colleagues (Benekareddy et al., 2010). In addition, RSK also modulates patterns of agonist functional selectivity (Strachan et al.). Thus genetic deletion of RSK2 in a similar cellular background (mouse embryonic

fibroblasts) led to profound alterations in patterns of agonist functional selectivity. These results demonstrated that deletion of a single GPCR kinase can profoundly affect functional selectivity and highlights the importance of cellular background as a key modulator of apparent patterns of agonist functional selectivity.

5-HT_{2A} receptors also interact with caveolin-1 (Bhatnagar et al., 2004), arrestins (Gelber et al., 1999; Gray et al., 2003) and microtubule associated proteins (MAPs) (Cornea-Hebert et al., 2002). This interaction of caveolin-1 is interesting in light of a recent report that deletion of caveolin-1 is a rare genetic cause of schizophrenia (Walsh et al., 2008). The interaction with caveolin-1 has been demonstrated by several groups to be essential for the functional activity of 5-HT_{2A} receptors (Dreja et al., 2002; Bhatnagar et al., 2004; Cogolludo et al., 2006; Sommer et al., 2009). It is not yet known if interactions with caveolin-1 modulate agonist or antagonist patterns of functional selectivity. The interaction of 5-HT_{2A} receptors with MAPs has been demonstrated by several groups (Cornea-Hebert et al., 2002; Maurer et al., 2004; Touri et al., 2004) and has been suggested to be essential for the polarized sorting of 5-HT_{2A} receptors (Cornea-Hebert et al., 2002; Allen et al., 2008b).

The interaction of 5-HT_{2A} receptors with arrestins (Gelber et al., 1999) which occurs in a cell-type-specific manner (Bhatnagar et al., 2001; Gray et al., 2001; Gray et al., 2003; Schmid et al., 2008), appears essential for arrestin-ergic signaling (Schmid et al., 2008) and receptor desensitization and internalization (Gray et al., 2001; Hanley and Hensler, 2002; Abbas and Roth, 2008a). Importantly, Laura Bohn's group has demonstrated that arrestin appears to be an essential mediator for the functionally-selective actions of certain 5-HT_{2A} agonists *in vitro* and *in vivo* (Schmid et al., 2008) (Fig 2).

2.4 Paradoxical regulation of 5-HT_{2A} receptors as a prototypic example of functional selectivity

For more than 30 years it has been known that some antagonists can down-regulate cortical 5-HT_{2A} radioligand binding *in vivo* (Bergstrom and Kellar, 1979; Peroutka and Snyder, 1980)—a finding which has been widely replicated see (Gray and Roth, 2001) for review. Such 'down-regulation' of 5-HT_{2A} receptors occurs without changes in 5-HT_{2A} mRNA (Roth et al., 1990; Roth and Ciaranello, 1991) and is accompanied by apparent 5-HT_{2A} receptor internalization (Willins et al., 1999). Selected antipsychotic and antidepressant drugs can induce a decrease in 5-HT_{2A} radioligand binding after chronic administration (Bergstrom and Kellar, 1979; Peroutka and Snyder, 1980; Mikuni and Meltzer, 1984; Andree et al., 1986), although this is not a characteristic of all drugs in these classes (Brunello et al., 1982; Barbaccia et al., 1983). Given the pharmacological promiscuity of many antipsychotic and antidepressant medications (Roth et al., 2004), it has been unclear whether the ability of these compounds to induce 5-HT_{2A} receptor down-regulation was due to direct action at 5-HT_{2A} receptors or via some other molecular target(s) (Leysen, 1990) (Roth et al., 1990). It is notable that not all 5-HT_{2A} antagonists will induce receptor down-regulation (Gandolfi et al., 1985) (Dave et al., 2007; Aloyo et al., 2009). Indeed, the relatively selective 5-HT_{2A} antagonist SR46349B reliably induces receptor up-regulation and sensitization *in vitro* and *in vivo* (Rinaldi-Carmona et al., 1993; Rinaldi-Carmona et al., 1994). Studies with several more selective compounds *in vitro* (Willins et al., 1998; Willins et al., 1999; Bhatnagar et al., 2001) have indicated that 5-HT_{2A} antagonists can induce 5-HT_{2A} receptor internalization via a dynamin-dependent, arrestin-independent mechanism which involves the clathrin-coated pit-endosome pathway (Berry et al., 1996; Willins et al., 1998; Willins et al., 1999; Bhatnagar et al., 2001) (Fig 3).

According to classical concepts of pharmacology, antagonists occupy receptors but do not "activate" the receptor complex in any way (Urban et al., 2007). Chronic antagonist exposure *in vivo* has been demonstrated in classic experiments to lead to receptor up-

regulation and a *sensitization* of receptor signaling (Schulz et al., 1979; Aarons et al., 1980; Zukin et al., 1982), rather than down-regulation as is the case for many 5-HT_{2A} antagonists. To explain this apparently paradoxical regulation of 5-HT_{2A} receptors, we proposed that “selective agonists and antagonists might be developed which have specific effects on a particular receptor-linked effector system...” (Roth and Chuang, 1987b) and that some of these ‘antagonist’ actions might include receptor down-regulation.

This notion that GPCR-effector systems might be extraordinarily complex and that drugs might be developed which have bias for distinct effector pathways has evolved into the concept of functional selectivity. Our current understanding of functional selectivity derives from classic experiments performed by William Clarke, Kelly Berg and colleagues on serotonin receptors (Berg et al., 1998), Kenakin and colleagues on peptide receptors (Kenakin, 1995) and Mailman and colleagues on dopamine receptors (Kilts et al., 2002; Mottola et al., 2002). Functional selectivity is now conceptualized as a process by which “ligands induce unique, ligand-specific receptor conformations that frequently can result in differential activation of signal transduction pathways associated with that particular receptor” (Urban et al., 2007). According to this conceptual model, then, down-regulating ‘antagonists’ are simply drugs which have a biased ability to induce receptor internalization and down-regulation without activation of canonical G-protein dependent- and –independent pathways. Thus, rather than being ‘paradoxical’ antagonist-induced down-regulation should perhaps be considered a special example of functional selectivity. Whether antagonist-induced 5-HT_{2A} receptor down-regulation is therapeutically-relevant is unknown and the subject of intensive study.

3.0 Future Directions

As can be seen from the foregoing, 5-HT_{2A} serotonin receptors continue to be important therapeutic targets for a number of diseases both within and outside the central nervous system (Berger et al., 2009). 5-HT_{2A}-selective compounds including M100907 (volinanserin), SR46349B (epilivanserin), pimavanserin and Org 50081 are currently being evaluated/have been evaluated for a number of therapeutic indications including sleep maintenance (<http://clinicaltrials.gov/ct2/results?term=m100907>) and insomnia (<http://clinicaltrials.gov/ct2/results?term=sr46349b>), psychosis related to Parkinson’s Disease (<http://clinicaltrials.gov/ct2/results?term=pimavanserin>), vasomotor symptoms (<http://clinicaltrials.gov/ct2/show/NCT00560833?term=5-ht2&rank=8>) respectively. It is also evident that the early views of serotonin-linked signal transduction were overly simplistic as there is now evidence for a plethora of signal-transduction pathways (both canonical and non-canonical) being essential for the *in vivo* actions of 5-HT_{2A} receptors (Abbas and Roth, 2008a) (Allen et al, *in press*). In particular, the recognition that agonists and antagonists can induce differential patterns of 5-HT_{2A} receptor functional selectivity (Roth and Chuang, 1987a; Berg et al., 1998; Willins et al., 1999; Kurrasch-Orbaugh et al., 2003) has opened up the potential for pathway-selective agents as novel therapeutics (Elphick et al., 2004; O’Connor and Roth, 2005; Urban et al., 2007). In the future, it will be significant to determine if pathway-selective agents represent superior therapeutics.

Additionally, it has become clear that the neuronal cell biology of 5-HT_{2A} receptors is exceedingly complex. A large number of PDZ-domain (PSD-95, Mupp-1) and non-PDZ-domain-containing proteins (Arf-1, caveolin, RSK2, MAPs) display functional interactions with 5-HT_{2A} receptors. As some of these interacting proteins are deleted in human disease (e.g. Caveolin-1 in schizophrenia and RSK2 in Coffin-Lowry Syndrome), it is possible that these interactions are significant contributors to the etiology of a variety of CNS diseases.

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Figure 1. RSK2 phosphorylates 5-HT_{2A} receptors to induce a ‘tonic brake’ on signaling
Shown is our current understanding of the molecular details responsible for RSK2-mediated attenuation of 5-HT_{2A} signaling. According to our current concepts, RSK2 tonically phosphorylates 5-HT_{2A} receptors at a nonconserved serine residue in the i3 loop (S314) via growth-factor-mediated activation (Strachan et al, 2009a, 2009b; Strachan et al 2010).

Figure 2. 5-HT_{2A} receptors and functional selectivity

Shown are three-dimensional cartoons of three distinct receptor conformations stabilized by distinct agonists. As shown, drugs (both ‘agonists’ and ‘antagonists’) can stabilize distinct receptor conformations leading to biased interactions with various down-stream effectors. The down-stream effector pathways are indicated by arrows going from the three dimensional receptor cartoons. These effector pathways can include canonical (G-protein dependent) and non-canonical (arrestin-ergic, scaffolding protein –dependent) signaling. As is shown, two different canonical pathways are demonstrated on the right (PKC activation; Ca⁺⁺ release) and left (kinase and channel activation) with arrestin-ergic signaling shown in the middle.

Figure 3. Paradoxical regulation of 5-HT_{2A} receptors

Shown is our current understanding of the cellular mechanisms by which agonists and antagonists can induce receptor internalization and down-regulation. Both agonists and antagonists internalize 5-HT_{2A} receptors via the endosome-clathrin coated pit pathway. Whether arrestins are crucial scaffolds for internalization is cell-type specific. Once receptors are internalized they may be recycled to the cell surface or, following chronic drug exposure, degraded via lysosomes and, perhaps, other pathways (e.g. ubiquitination).