Published in final edited form as:

Curr Psychiatry Rep. 2008 October ; 10(5): 377–384.

Use of Animal Models to Develop Antiaddiction Medications

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Abstract

Although addiction is a uniquely human phenomenon, some of its pathognomonic features can be modeled at the animal level. Such features include the euphoric “high” produced by acute administration of addictive drugs; the dysphoric “crash” produced by acute withdrawal, drug-seeking, and drug-taking behaviors; and relapse to drug-seeking behavior after achieving successful abstinence. Animal models exist for each of these features. In this review, I focus on various animal models of addiction and how they can be used to search for clinically effective antiaddiction medications. I conclude by noting some of the new and novel medications that have been developed preclinically using such models and the hope for further developments along such lines.

Introduction

Addiction is a uniquely human disease largely defined by human behaviors that are difficult to fully model at the animal level. Although addiction has been equated with physical dependence in past decades, this only served to confuse terminology within the field. Physical dependence is produced by many classes of drugs with no addictive liability (eg, antidepressants, cardiac medications, corticosteroids, diabetic agents). Unfortunately, physical dependence and the “drug-opposite” withdrawal effects produced by abrupt cessation or rapid dose reduction [1•] have often been considered the hallmarks of addiction. This has spread so far as to influence the *DSM* [2], in which addiction is termed *dependence*. This is wrong and confusing [3]. Drug addiction is a behavioral and mental disorder characterized by impaired control over drug self-administration, compulsive drug self-administration, continued drug self-administration despite obvious harm to self and significant others, and drug craving. Thus, addiction is often termed the *disease of the 5 “Cs”*: chronic disease with impaired control, compulsive use, continued use despite harm, and drug craving. The drug-taking behavior is habit based and depends critically upon learning and memory processes [4]. Equally important, drug addiction is driven primarily by the pleasurable or rewarding effects of addictive drugs—the “high” [5•]. Although drug taking is also driven by a desire to ward off unpleasant withdrawal symptoms in some cases, pursuit of the “high” remains the goal.

Because addiction is a uniquely human phenomenon, animal models can only approximate its features. Additionally, each model attempts to capture only one specific aspect of addiction, such as the drug-induced reward, the drug-seeking behavior, the drug-taking behavior, and various aspects of relapse to drug seeking and drug taking. Also, because considerable progress in recent decades has revealed a great deal about the brain circuitry and mechanisms underlying addiction’s behavioral features, some animal models probe those underlying brain substrates at the electrophysiologic, neurochemical, cellular biologic, and/or molecular biologic levels.

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Disclosure

No potential conflict of interest relevant to this article was reported.

Brain Mechanisms Underlying Addiction

It is well established that the acute “high,” “hit,” or “rush” that addictive drugs produce refers to activation of mesolimbic dopamine (DA) reward circuits in the ventral forebrain [5•]. These reward circuits run “in series” and consist of three major components. The first component originates in the anterior bed nuclei of the medial forebrain bundle (MFB); axons from these nuclei join together and run caudally within the MFB to synapse upon DA cell bodies in the ventral tegmental area (VTA). The second component consists of DA fibers originating within the VTA and running rostrally within the MFB to synapse in the nucleus accumbens (Acb), olfactory tubercle, medial prefrontal cortex, and amygdala. The third component consists of medium spiny γ -aminobutyric acid (GABA)-ergic neurons that colocalize an endogenous opioid peptide and run from the Acb to the ventral pallidum (Fig. 1). Electrical brain-stimulation reward preferentially activates the caudally running component within the MFB [6], whereas addictive drugs preferentially activate the rostrally running DA component [7]. Conversely, withdrawal from addictive drugs inhibits the brain reward substrates and extracellular DA at reward-relevant synapses in the Acb.

Relapse to drug use triggered by re-exposure to addictive drug appears to be mediated by a portion of the VTA-Acb DA pathway [8]. Relapse triggered by stress appears to be mediated by two separate brain circuits: a noradrenergic circuit arising in the lateral tegmental area of the brain stem and projecting rostrally to the hypothalamus, bed nucleus of the stria terminalis, Acb, and amygdala, and a circuit using corticotropin-releasing factor as its neurotransmitter that arises in the central nucleus of the amygdala and projects to the bed nucleus of the stria terminalis [8]. Relapse triggered by re-exposure to environmental cues previously associated with addictive drug use appears to be mediated by two glutamatergic circuits: one arising in the ventral subiculum of the hippocampus and the other arising in the lateral complex of the amygdala, both of which project to the Acb (Fig. 1) [8].

Drug craving is a complex phenomenon involving cognitive and affective processes and is unlikely to be a unitary construct (with different types of craving dependent upon perceived drug use opportunity) [9]. At present levels of understanding, most types of drug craving appear to involve activation within the Acb, orbitofrontal cortex, anterior cingulate cortex, and dorsolateral caudate nucleus [10,11].

Animal Models Relevant to Addiction

Addiction almost invariably starts with seeking the pleasurable “high” produced by addictive drugs and is also at least in part maintained by that motivation. Therefore, animal models that assess the degree to which drugs of abuse enhance brain reward and the degree to which putative therapeutic medications attenuate that enhancement have a role in developing antiaddiction medications.

Electrical brain-stimulation reward

The standard laboratory animal model for assessing brain reward function is that of electrical brain-stimulation reward [5•]. In this model, stimulating electrodes are surgically implanted into the brain’s reward circuitry, and animals are allowed to volitionally operate a manipulandum (eg, pressing a wall-mounted lever in the test chamber, poking their nose into a recess, and thus breaking a photo beam; rotating a wall-mounted wheel) connected to a brain stimulator to self-deliver brief trains of electrical stimulation. Such electrical brain stimulation is intensely rewarding and summates with the reward produced by addictive drugs. Thus, by measuring the threshold for rewarding brain stimulation, one can assess the degree to which a substance is rewarding or pleasurable. Conversely, one can also measure the degree of dysphoria produced by withdrawal from addictive drugs. In this model, a promising

antiaddiction medication would be expected to attenuate the euphorogenic “high” produced by addictive drugs and the dysphorigenic “crash” produced by acute withdrawal.

In vivo brain microdialysis

As enhanced DA function in the VTA-Acb axis is believed to be the neurochemical substrate for the “high” produced by addictive drugs, another useful laboratory animal model is in vivo brain microdialysis for assessing extracellular DA overflow in the reward-related Acb [12]. In this model, a small probe constructed of stainless steel and microdialysis tubing with separate inlet and outlet channels is surgically implanted into the Acb. The probe is constructed in such a way that the microdialysis tubing is unoccluded only within the Acb. Artificial cerebrospinal fluid is pumped at a slow perfusion rate through the probe and out to a chemical analytical device, typically a high-pressure liquid chromatograph. DA within the local drainage area of the probe (typically ~ 1 mm in diameter) crosses the membrane into the probe and is carried out to the chemical analytical device. In this manner, real-time assays of DA levels within the reward-relevant Acb (or Acb subdomains such as shell and core) are obtained. In this model, a promising antiaddiction medication would be expected to attenuate the enhanced Acb DA produced by addictive drugs and the diminished DA produced by withdrawal.

In vivo voltammetric electrochemistry

Another useful laboratory animal model for assessing real-time extracellular DA overflow in the reward-related Acb is in vivo voltammetric electrochemistry [12]. This technique rests upon the fortuitous chemical coincidence that DA is electrooxidizable, yielding an oxidation current proportional to the amount of DA at the tip of the detector electrode. In this model, a needle-shaped detector microelectrode is fabricated and surgically implanted into the Acb. Using techniques analogous to classical voltage-clamp electrophysiology, an electrical potential is applied, and the resulting oxidation and reduction currents are measured. Identification of the chemical being measured is made by several strategies, including the electrical potential at which the oxidation peak occurs, characteristic oxidation/reduction ratios, and the characteristic “signature” of the voltammogram in cyclic voltammetry. Although identification of the chemical species being measured is less certain than with microdialysis, voltammetric electrochemistry is faster and allows for more anatomic precision because the electrodes used are at least a full order of magnitude smaller than the smallest microdialysis probe. As with microdialysis, in this model, a promising antiaddiction medication is expected to attenuate the enhanced Acb DA produced by addictive drugs and the diminished DA produced by withdrawal.

Conditioned place preference

Among the behavioral animal models of addiction, conditioned place preference [13,14•] is widely used and considered a model of environmental stimuli’s ability to acquire incentive motivational properties by virtue of being paired with drug exposure. This model uses a test apparatus that is little more than a simple, two-chambered box with a removable barrier between the two chambers. The two chambers have distinctly different environmental cues (eg, differently patterned walls, differently textured floors, different smells) that are initially motivationally neutral (ie, the animal shows no initial preference for one chamber over the other). Animals are given drug injections and then confined to one chamber on some days and given vehicle injections and confined to the other chamber on other days. On test days, the animals are given free choice between the two chambers, and time spent in each chamber is measured. If the animal chooses the drug-paired chamber, the inference is that the animal enjoyed the drug experience. If the animal avoids the drug-paired chamber, the drug experience is inferred to have been aversive. The unpleasant experience of withdrawal also produces a conditioned place aversion in this model. This is a Pavlovian paradigm, because the drug is

administered in a response-independent manner. In this model, a promising antiaddiction medication would be expected to at least attenuate conditioned place preference produced by addictive drugs, and, ideally, the conditioned place aversion produced by drug withdrawal.

Drug self-administration paradigm

The drug self-administration paradigm [15] offers seemingly the most face-relevant animal model of addiction. This is an instrumental paradigm, in that the animal must respond instrumentally (eg, lever-pressing, wheel-turning, nose-poking) to receive the drug. The drug can be delivered via many routes, but intravenous and oral are the most common. Although this model is most often used with fixed-ratio reinforcement contingencies, other reinforcement contingencies can be used and produce interesting variants of the model that are important enough to be described separately below. In the self-administration model, a promising antiaddiction medication would be expected to attenuate self-administration of addictive drug(s) while, ideally, not altering instrumental responding for natural, biologically essential rewards (eg, food, sex).

Progressive-ratio break point model

An interesting and useful variant of the self-administration model is the progressive-ratio break point model [16], in which a progressively increasing workload is imposed upon the animal to receive a drug injection during a test session. In every such session, a point is reached at which the animal's instrumental responding for drug drops below some criterion level (often an abrupt cessation of responding): the progressive-ratio break point. This break point is taken as a measure of reinforcing efficacy. When properly implemented, progressive-ratio break point estimates of the reward value of addictive drugs closely parallel the verbal rank ordering of drug "appeal" given by experienced polydrug-abusing humans [17]. In this model, a promising antiaddiction medication would be expected to decrease the break point for self-administration of addictive drug(s) (ie, to reduce reward value). Ideally, a promising antiaddiction medication would not decrease the break point for (ie, the appeal of) natural, biologically essential rewards (eg, food, sex).

Second-order reinforcement drug self-administration

Conditioned reinforcement paradigms are hybrid behavioral paradigms in that they involve instrumental and Pavlovian conditioning. These paradigms involve animals responding instrumentally (eg, lever-pressing, wheel-turning, nose-poking) to receive presentation of a cue stimulus (eg, light, tone) that has been paired previously with drug reward and therefore acquired the rewarding drug's incentive motivational properties. One example of a conditioned reinforcement paradigm that figures prominently in antiaddiction medication development is second-order reinforcement drug self-administration [18]. In this model, the animal is allowed to self-administer drug, with a distinctive environmental cue (eg, light, tone) paired with each injection. The animal is then tested under extinction conditions with the drug reinforcer no longer available. Animals work for presentation of such an environmental cue, from which it is inferred that the cue has acquired incentive motivational value (as in the conditioned place preference model previously described). After adequate training under second-order reinforcement, a lengthy response sequence is maintained by intermittent presentations of the cue. A typical second-order reinforcement schedule may require an animal to emit 30 responses to receive the cue presentation-conditioned stimulus, with the drug primary reinforcer being given after the 30th response emitted after 1 hour of responding has elapsed. The major virtue of second-order reinforcement drug self-administration is that responding for drug reinforcement can be maintained for prolonged periods before the actual delivery of drug. This disambiguates drug-seeking behavior from drug-taking behavior and is uncontaminated by cumulative drug effects [19]. In this model, a promising antiaddiction medication would be

expected to attenuate cue-maintained drug-seeking behavior while, ideally, not altering cuemaintained drug-seeking behavior for natural, biologically essential rewards (eg, food, sex).

Reinstatement model of relapse to drug-seeking behavior

Another hybrid (instrumental and Pavlovian) paradigm is the reinstatement model of relapse to drug-seeking behavior [20]. As relapse is the major clinical problem in addiction medicine, this model has high appeal for medication development [21]. In this model, the animal is allowed to self-administer drug to a high criterion of drug-taking behavior and is then subjected to behavioral extinction (ie, tested under conditions of nonreinforcement until the drug-seeking behavior is extinguished [reduced to a strict criterion of nonresponse]). Various stimuli are then presented, and the animal's drug-seeking behavior (the instrumental response that previously yielded drug) is measured. A stimulus is said to "reinstatement" the drug-seeking behavior if it causes renewed responding despite the absence of further drug reward. The three classical triggers to relapse [22] at the human level—re-exposure to addictive drug, stress, and re-exposure to environmental cues ("people, places, things") previously associated with drug-taking behavior—are the three triggers to relapse in this animal model [23]. In this model, a promising antiaddiction medication would be expected to attenuate reinstatement, with the most promising medications expected to attenuate all three forms of reinstatement: drug-triggered, stress-triggered, and cue-triggered. At the same time, ideally, a promising antiaddiction medication would be expected to not attenuate reinstatement of reward-seeking behavior for natural, biologically essential rewards (eg, food-triggered reinstatement of food-seeking behavior).

Conflict model of relapse

A recently developed variant of the reinstatement model of relapse is the conflict model of relapse [24]. This model is predicated on the fact that in the reinstatement model, drug-seeking behavior is deliberately extinguished from the test animal's behavioral repertoire by nonreinforcement of the drug-seeking behavior, whereas in humans, abstinence is often self-imposed as a direct result of the adverse consequences of drug taking. The conflict model seeks to emulate the human situation by using adverse consequences (painful foot shock) to eliminate drug-seeking behavior in animals. After the behavior has been eliminated, drug seeking is reinstated by presentation of relapse triggers, as in the reinstatement model. Thus far, it has been established that drug-paired environmental cues trigger relapse in the conflict model; evidence for drug-triggered or stress-triggered relapse in this model is not yet forthcoming. In this model, a promising antiaddiction medication would be expected to attenuate reinstatement of drug-seeking behavior, ideally without attenuating reinstatement of reward-seeking behavior for natural rewards. This new model probably will become part of the preclinical armamentarium of medication development only if it can be demonstrated to be as useful for drug- and stress-triggered relapse as it currently appears to be for cue-triggered relapse.

Reactivation paradigm

Yet another animal model of relapse is the reactivation paradigm [25]. In this model, a drug-induced conditioned place preference is established and then extinguished. After extinction, various triggers reactivate the place preference. Such reactivation has been reliably demonstrated using drug triggers [25] and stress triggers [26]. Among the latter, a variety of stressors are effective, including physical stress (eg, foot shock [26], restraint [27], tail pinch [27], forced swimming [28]), social stress (eg, social defeat [27]), and environmental cue stress (eg, withdrawal-associated aversive environmental cues [29], conditioned fear stimuli [30]). In this model, a promising antiaddiction medication would be expected to attenuate reactivation of drug-seeking behavior (ie, seeking the previously drug-paired compartment in the

conditioned place preference apparatus), ideally without attenuating reactivation of reward-seeking behavior for natural rewards.

Straight-alley runway drug self-administration paradigm

One final animal model is worthy of mention: the straight-alley runway drug self-administration paradigm [31]. In this model, an animal is required to run down a straight alley from a start box to a goal box, wherein an addictive drug is administered. This drug self-administration model's merit is that it seems to be uniquely sensitive to addictive drugs' appetitive and aversive properties. Animals running for cocaine reward once a day in this model develop an approach-avoidance conflict about entering the goal box (ie, they approach and retreat from the goal box many times during a single run). This behavior is interpreted as reflecting cocaine's appetitive and aversive properties. In this model, a promising antiaddiction medication may be expected to attenuate the approach behavior while, optimally, intensifying the avoidance behavior prompted by drug reward. As in other models, neutrality with respect to affecting approach behavior for natural rewards would seem optimal.

Use of Animal Models in Antiaddiction Medication Development

I now illustrate the use of animal models in antiaddiction medication development by citing their use in developing possible antiaddiction pharmacotherapies based on three different pharmacotherapeutic strategies.

Slow-onset, long-acting DA transporter blockers

This strategy is based on the hypotheses that vulnerability to addictive drugs may derive in part from pathologic hypofunctionality of DA neurons in the reward-related VTA-Acb neural system [32] and that speed of addictive drug action on Acb DA correlates positively with addictive potency [33]. Therefore, slow-onset, long-acting DA transporter blockers have been developed as potential antiaddiction medications, with a wide variety of chemical structures: tropanes, benzotropines, mazindol-like compounds, substituted piperazines, indanamines, and trans-aminotetralines.

Our own work with indanamines and trans-aminotetralines illustrates this approach [34-37]. Several indanamine analogue DA transporter blockers enhance Acb DA in slow-onset, long-acting fashion; enhance electrical brain-stimulation reward; and decrease intravenous cocaine self-administration in laboratory rats that cannot sustain self-administration themselves [34, 35]. Trans-aminotetraline derivatives also have been tested in animal models, with promising findings (ie, slow-onset, long-acting enhancement of Acb DA; electrical brain-stimulation reward, and dose-dependent reductions in cocaine self-administration) [36,37].

GABA-mimetic compounds acting at the GABA_B receptor

This strategy is based on the following: 1) GABA-ergic afferents innervate and modulate the brain's reward and relapse circuitry, 2) Acb GABA-ergic output neurons may constitute a brain reward final common pathway, 3) microinjections of the GABA_B receptor agonist baclofen into the VTA inhibit VTA-Acb DA reward functions, and 4) acquisition and expression of conditioned emotional responses (eg, drug craving) may involve Acb GABA-ergic function.

Therefore, animal models have been used to investigate whether GABA-mimetic compounds have potential as antiaddiction pharmacotherapies. We focused on the irreversible GABA transaminase inhibitor γ -vinyl-GABA (GVG) and found that it dose-dependently attenuates enhanced Acb DA produced by cocaine, nicotine, methamphetamine, heroin, ethanol, or a cocaine/heroin ("speedball") combination [38], and antagonizes augmented Acb DA produced by drug-associated environmental cues [39]. GVG also attenuates cocaine's enhancement of

electrical brain-stimulation reward [40], blocks heroin or cocaine self-administration [41], and lowers the progressive-ratio break point for cocaine self-administration [42]. Recently, we have shown that GVG inhibits cocaine-triggered relapse to drug-seeking behavior using the reinstatement model [43].

Similar work has focused on the selective GABA_B agonist baclofen. Baclofen dose-dependently reduces opiate- or cocaine-enhanced Acb DA [43,44] and cocaine-enhanced brain-stimulation reward [45]. Baclofen dose-dependently attenuates intravenous opiate or cocaine self-administration [41,46], reduces progressive ratio break points for such self-administration [46], and reduces cocaine-seeking behavior under second-order reinforcement [47]. It also blocks heroin- and cocaine-triggered relapse to drug-seeking behavior in the reinstatement model [46].

Selective DA D₃ antagonists

A third medication development strategy for addiction treatment that owes its existence to the animal models discussed previously is that of highly selective DA D₃ receptor antagonists. This strategy is based on the following: 1) the hypothesis that VTA-Acb DA hypofunctionality may contribute to addiction vulnerability [32], 2) that the DA D₃ receptor shows preferential localization in the VTA-Acb reward and relapse system, 3) that D₃ receptor inhibition activates the VTA-Acb DA system, and 4) the suggestion that the D₃ receptor plays a role in the reinforcement produced by addictive drugs [48•]. These considerations have prompted the study of compounds acting on the DA D₃ receptor system in animal models of addiction. Such studies were initially hampered by lack of D₃-selective compounds, until the development of trans-N-[4-[2-(6-cyano-1,2,3,4-tetrahydroisoquinolin-2-yl)ethyl]cyclohexyl]-4-quinolininecarboxamide (SB-277011A), a novel brain-penetrant, highly selective D₃ receptor antagonist with 80-fold to 100-fold selectivity over DA D₂ receptors and 180 other central nervous system receptors, transporters, enzymes, and ion channels [48•].

In preclinical tests with many of the animal models mentioned previously, we have shown that SB-277011A shows a remarkably promising profile [48•]. Specifically, SB-277011A attenuates cocaine- or methamphetamine-enhanced electrical brain-stimulation reward; attenuates acquisition and expression of opiate- or cocaine-induced conditioned place preference; produces a pronounced downshift in the break point (ie, reduces motivation) for intravenous cocaine or methamphetamine self-administration under progressive-ratio reinforcement conditions; attenuates cocaine-seeking behavior under second-order reinforcement conditions; attenuates cocaine-triggered, stress-triggered, or environmental cue-triggered relapse to cocaine-seeking behavior in the reinstatement paradigm; and attenuates ethanol self-administration in laboratory rats and mice [48•]. SB-277011A also attenuates nicotine-enhanced electrical brain-stimulation reward, nicotine-induced conditioned place preference, and nicotine-paired environmental cue functions [49]. Corroborative evidence that SB-277011A's remarkably broad profile of antiaddiction properties in a wide variety of preclinical animal models is due to its DA D₃ receptor antagonist properties rather than to some other idiosyncratic pharmacologic property is based upon the similar pattern of animal model findings from another highly selective DA D₃ receptor antagonist: NGB-2904 [50•]. Arguably, SB-277011A has been shown to have a promising antiaddiction, anticraving, and antirelapse profile in a broader range of addiction-related animal models than any other putative pharmacotherapeutic agent in the history of addiction medicine [48•], although GVG and baclofen also have been screened in a broad array of animal models. On a cautionary note, neither SB-277011A nor NGB-2904 attenuates intravenous cocaine self-administration under low-effort (ie, low fixed-ratio reinforcement) or high-payoff (large amounts of cocaine per reinforcement) conditions [48•,50•]. Despite this caution, the overall profile of SB-277011A and NGB-2904 in animal models of addiction suggests potential use for DA D₃ antagonists as

antiaddiction pharmacotherapies. As a direct result of this work, development of new D₃-selective antagonists as antiaddiction medications continues.

Conclusions

The use of preclinical animal paradigms that model some of the features of addictive disease has yielded promising potential antiaddiction, anticraving, antirelapse medications. Their success or failure at the human level will provide vital information regarding the predictive validity of said preclinical animal models.

Acknowledgments

Preparation of this manuscript was supported by the Intramural Research Program, National Institute on Drug Abuse, National Institutes of Health, US Public Health Service. Some of the research work cited from the author's own laboratory was supported by the National Institute on Drug Abuse, the Aaron Diamond Foundation, the Julia Sullivan Medical Research Fund, and the New York State Office of Alcoholism and Substance Abuse Services.

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Figure 1.

Midsagittal diagram of the mammalian (laboratory rat) brain showing brain circuitry involved in mediating drug-induced reward, drug-seeking behavior, drug-taking behavior, drug craving, and relapse to drug-seeking behavior. Sites at which various addictive drugs act to enhance brain reward substrates are indicated. The principal circuit mediating drug-induced reward is the dopamine (DA) circuit originating in the ventral tegmental area (VTA) and projecting to the nucleus accumbens (Acb). The principal circuit mediating drug-induced stimulus-response and stimulus-reward learning involves the VTA, Acb, prefrontal cortex (FCX), and amygdala (AMYG). The principal circuit mediating drug-triggered relapse to drug-seeking behavior involves the Acb. Two principal circuits mediate stress-triggered relapse to drug-seeking behavior: one involving the lateral tegmental noradrenergic cell groups (LAT-TEG) and their projections to the hypothalamus (HYPOTHAL), bed nucleus of the stria terminalis (BNST), Acb, and AMYG and one involving corticotropin-releasing factor (CRF) cell groups in the AMYG and their projections to the BNST. The principal circuitry mediating cue-triggered relapse to drug-seeking behavior involves glutamatergic cell groups in the AMYG and hippocampus (HIPP) and their projections to the VTA-Acb DA pathway. 5HT—5-hydroxytryptamine (serotonin); ABN—anterior bed nuclei of the medial forebrain bundle; BSR—electrical brain-stimulation reward; DYN—dynorphin; END—endorphin; ENK—enkephalin; GABA— γ -aminobutyric acid; GLU—glutamate; LC—locus coeruleus; NE—norepinephrine (noradrenaline); OFT—olfactory tubercle; OPIOID—endogenous opioid; PAG—periaqueductal gray matter; Raphé—Raphé nuclei of the brain stem; RETIC—reticular formation of the brain stem; VP—ventral pallidum.