HHS Public Access

Author manuscript

Pharmacol Ther. Author manuscript; available in PMC 2019 June 01.

Published in final edited form as:

Pharmacol Ther. 2018 June ; 186: 152–167. doi:10.1016/j.pharmthera.2018.01.009.

The Sigma-1 Receptor as a Regulator of Dopamine Neurotransmission: A Potential Therapeutic Target for Methamphetamine Addiction

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Abstract

Methamphetamine (METH) abuse is a major public health issue around the world, yet there are currently no effective pharmacotherapies for the treatment of METH addiction. METH is potent psychostimulant that increases extracellular dopamine levels by targeting the dopamine transporter (DAT) and alters neuronal activity in the reward centers of the brain. One promising therapeutic target for the treatment of METH addiction is the sigma-1 receptor (σ_1R). The σ_1R is an endoplasmic reticulum-localized chaperone protein that is activated by cellular stress, and, unique to this chaperone, its function can also be induced or inhibited by different ligands. Upon activation of this unique "chaperone receptor", the σ_1R regulates a variety of cellular functions and possesses neuroprotective activity in the brain. Interestingly, a variety of σ_1R ligands modulate dopamine neurotransmission and reduce the behavioral effects of METH in animal models of addictive behavior, suggesting that the σ_1R may be a viable therapeutic target for the treatment of METH addiction. In this review, we provide background on METH and the σ_1R as well as a literature review regarding the role of σ_1Rs in modulating both dopamine neurotransmission and the effects of METH. We aim to highlight the complexities of σ_1R pharmacology and function as well as the therapeutic potential of the σ_1R as a target for the treatment of METH addiction.

Keywords

sigma-1 receptor; dopamine; dopamine transporter; methamphetamine

1. INTRODUCTION

Methamphetamine (METH) is one of the most commonly used illicit drugs in the world (Krasnova and Cadet, 2009), with reports that up to 35 million people use amphetamine-type stimulants (ATSs) worldwide (Salamanca et al., 2014). Although there have been clinical

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7. CONFLICT OF INTEREST STATEMENT

The authors declare that there are no conflicts of interest.

trials for drugs targeting the dopaminergic, serotonergic, and opioid systems (Karila et al., 2010), there are currently no Food and Drug Administration (FDA) approved pharmacotherapies for the treatment of METH addiction (Napier et al., 2013). While it is well established that METH elicits its addictive effects primarily through interactions with the dopamine transporter (DAT) (Sulzer et al., 1993), growing evidence indicates that sigma receptors (σRs) may be involved in METH addiction. Two isoforms of σRs are known to exist, σ_1R and σ_2R; however, the σ_1R has been more thoroughly characterized in the literature (Bowen, 2000; Quirion et al., 1992). In addition to responding to cellular stress, the σ_1R is a ligand-operated chaperone protein that can be activated or inhibited by different ligands in an agonist-antagonist manner (Hayashi and Su, 2003b; Tsai et al., 2009). Several σ_1R-targeting drugs are proposed as possible treatments for human diseases including neurodegeneration, psychiatric disorders, neuropathic pain, and drug abuse (Hayashi, 2015). Importantly, multiple FDA-approved drugs that are widely used for the treatment of schizophrenia and depression have high affinity for the σ_1R, supporting the therapeutic potential of drugs targeting σ_1Rs. While several studies have reported that σR ligands attenuate some of the behavioral effects of cocaine and METH in rodent models, the mechanisms by which σR ligands produce these effects are largely unknown. With the ongoing synthesis of novel, highly selective σ_1R ligands every year and the increased understanding of the protein's function, the σ_1R remains a highly attractive therapeutic target for METH addiction.

2. METHAMPHETAMINE

Patterns of Methamphetamine Use

Methamphetamine (METH) is a widely abused, highly addictive psychostimulant that belongs to a class of synthetic drugs called amphetamine-type stimulants (ATSs). This class includes amphetamine (AMPH), METH, methylenedioxy-methamphetamine (MDMA), and other designer drugs (Chomchai and Chomchai, 2015). AMPH and METH were once widely distributed as over-the-counter drugs for the myriad of "positive" effects that quickly became causative for their use (increased wakefulness, appetite suppression, etc.) (Vearrier et al., 2012). The intended beneficial use of these drugs, however, was offset by their highly addictive potential, ultimately leading to ATSs becoming among the most abused drugs in the world. The 2016 United Nations Office on Drugs and Crime World Drug Report estimated that over 35 million people use AMPHs and prescription stimulants across the world (UNODC, 2016). METH specifically has surpassed the other ATSs in popularity, production, and trafficking. While AMPH and METH share similar mechanisms of action as well as behavioral effects, the drugs have differing molecular structures and cellular effects (Goodwin et al., 2009; Saha et al., 2014), and METH is more commonly associated with recreational use and drug addiction. METH can be synthesized by the reduction of everyday over-the-counter nasal decongestants that contain ephedrine or pseudoephedrine, and the relative accessibility of these starting materials led to the expansion of small scale METH laboratories across the United States (Ciccarone, 2011; Panenka et al., 2013). Despite attempts to limit sales of these products with the 2005 Combat Methamphetamine Epidemic Act, larger-scale illicit METH manufacturers emerged (Maxwell and Brecht, 2011; SAMHSA, 2006). In 2014, there was a global peak in ATS law enforcement seizures

worldwide, with METH accounting for the largest share of ATS seizures increasing an estimated 21% from the previous year (UNODC, 2016). Despite widespread efforts to decrease METH production, METH use continues to be a major public health problem worldwide.

Effects of Methamphetamine Use

Upon administration, there are several acute physiological effects associated with METH use. By promoting the release of epinephrine and norepinephrine, METH acts as a potent stimulant by activating the sympathetic nervous system (Schneider, 1972). This provokes an array of responses including increased blood pressure, hyperthermia, tachycardia, increased breathing, pupil dilatation, peripheral hypertension, and reduced appetite (Courtney and Ray, 2014; Rawson and Condon, 2007). Non-essential physiological activities, such as gastrointestinal function, are inhibited (Panenka et al., 2013), and levels of stress hormones including cortisol and adrenocorticotrophic hormone can increase up to 200% (Harris et al., 2003). Most notably, METH administration also elicits a suite of reinforcing effects including euphoria, arousal, heightened awareness, reduced fatigue, behavioral disinhibition, positive mood, increased self-confidence, and acute cognitive improvement (Courtney and Ray, 2014). Conversely, METH can also induce acute negative psychological effects including anxiety, insomnia, aggressive behavior, paranoia, and psychosis (Rawson and Condon, 2007). At high doses, METH can elevate the body temperate to potentially lethal levels, resulting in convulsions, coma, stroke, or even death (Rawson and Condon, 2007).

Like other drugs of abuse, prolonged METH use often results in drug tolerance, typically leading to increased dosage and frequency of use (Rawson and Condon, 2007). Long-term chronic METH use often leads to the development of symptoms including violent behavior, anxiety, cognitive impairment, and insomnia (Rawson and Condon, 2007). Additionally, many chronic METH users report psychotic symptoms similar to those of schizophrenia, namely paranoia, auditory hallucinations, mood disturbances, delusions, and abnormal speech (Hsieh et al., 2014). Additional adverse physiological consequences of prolonged METH use include cardiovascular problems, pulmonary disease, and infections from repeated intravenous injections (such as HIV) (Rawson and Condon, 2007). Patterns of METH abuse may also lead to other negative repercussions including disrupted personal relationships, unemployment, and incarceration (Hsieh et al., 2014).

Methamphetamine Regulation of Extracellular Dopamine

The administration of ATSs results in an acute increase in the monoamines dopamine (DA), norepinephrine, and serotonin in the brain (Azzaro and Rutledge, 1973; Halpin et al., 2014). Both the rewarding and addictive properties of ATSs are primarily attributed to their ability to increase extracellular DA levels (Sonders et al., 1997). In both humans and animal models, blockade of DA receptors decreases the euphoric effects of AMPH, demonstrating the importance of DA in the rewarding effects of the drug (Davis and Smith, 1975; Gunne et al., 1972; Jonsson et al., 1971; Yokel and Wise, 1975). In 1988, Di Chiara and Imperato reported that while administration of cocaine, morphine, methadone, ethanol, and nicotine in rats increased extracellular DA levels in the striatum up to 400%, AMPH treatment increased extracellular DA levels up to 1000% (Di Chiara and Imperato, 1988),

demonstrating the profound capacity of ATSs to activate the DA system. Human imaging studies have similarly reported increased DA levels after the administration of amphetamines (Volkow et al., 2007; Volkow et al., 1999). The mechanism by which METH increases DA levels in the brain – a direct interaction with its primary target the dopamine transporter (DAT) - has been well characterized.

Methamphetamine Interactions with DAT

Dopamine (DA) is important for regulating processes including reward, motivation, movement, working memory, and cognition (Chinta and Andersen, 2005). The main source of DA in the brain is midbrain dopaminergic neurons, which includes the substantia nigra (SN) and ventral tegmental area (VTA). The dopamine transporter (DAT) is a transmembrane protein located on dopaminergic neurons that primarily functions to take up DA released into the extracellular space. Upon reuptake, dopamine can then be sequestered into synaptic vesicles via the vesicular monoamine transporter-2 (VMAT-2) for storage until the next exocytosis event (Giros et al., 1996). DAT knockout mice display hyperactivity, cognitive deficits, altered psychostimulant responses, and persistently high levels of extracellular DA with low tissue DA content (Giros et al., 1996), highlighting the requirement of DAT for regulating DA homeostasis as well as the actions of psychostimulants.

Both cocaine and ATSs increase extracellular DA levels through direct interactions with DAT. While cocaine increases extracellular DA levels by blocking DAT and preventing DA reuptake, METH interacts with DAT to increase extracellular DA levels through a variety of mechanisms (Figure 1). As a substrate for the transporter, METH enters DA neurons directly through DAT and consequently decreases DA uptake via competitive inhibition (Fleckenstein et al., 1997). Once inside the neuron, METH disrupts vesicular stores of DA, resulting in the release of DA into the cytoplasm of the neuron (Sulzer and Rayport, 1990). Importantly, METH also induces the reverse transport of DA from the cytosol to the extracellular space via DAT-mediated, action potential independent DA efflux (Sulzer et al., 1995). This is thought to occur via the facilitated exchange diffusion model in which forward transport of AMPHs is followed by a counter movement of DA outside the cell (Fischer and Cho, 1979; Khoshbouei et al., 2003). This model is supported by evidence showing that compounds that release DA from vesicular stores without affecting DAT activity do not produce DA efflux, demonstrating the importance of the inward transport of AMPH (Jones et al., 1998). This process is voltage-dependent and highly regulated by AMPH-induced increases in intracellular Na^+ and Ca^{2+} as well as proteins interacting with DAT (Khoshbouei et al., 2003).

Beyond competitive inhibition of DA uptake and reverse DA transport, ATSs also impact the electrophysiological properties of DA neurons through a DAT-dependent mechanism. AMPH-mediated DA release activates D_2 autoreceptors which inhibit the firing activity of DA neurons (Bunney et al., 1973). Pharmacological blockade of these autoreceptors, however, reveals AMPH-mediated increases in firing activity above baseline (Shi et al., 2000). This increase in firing activity is inhibited by DAT blockers, suggesting it occurs via a DAT-dependent mechanism (Ingram et al., 2002; Lin et al., 2016; Saha et al., 2014). DAT

also carries a channel-like current uncoupled to DA transport (DeFelice and Blakely, 1996; Kahlig et al., 2005; Lester et al., 1994). AMPHs increase this DAT-dependent inward positive current (Fischer and Cho, 1979; Saha et al., 2014) leading to membrane depolarization and increased firing activity of dopaminergic neurons. Importantly, previous studies revealed that repeated METH exposure in rodents decreases the sensitivity of D_2 autoreceptors, which in turn could increase METH-mediated, DAT-dependent firing activity (White and Wang, 1984; Wolf et al., 1993).

AMPHs are also known to internalize the transporter in a protein kinase C (PKC)-dependent manner. This is presumably via AMPH-induced increases in intracellular Ca^{2+} (Gnegy et al., 2004; Goodwin et al., 2009) that in turn activate PKC (Giambalvo, 1992), or AMPH-induced membrane depolarization (Richardson et al., 2016). By promoting DAT internalization, AMPHs decrease DA transport by limiting available DAT at the membrane for uptake (Cowell et al., 2000; Melikian and Buckley, 1999). Over the past several years, other signaling pathways involved in DAT trafficking have also been identified, including a role for Ca^{2+}/calmodulin-dependent protein kinase II, MAP/ERK, and membrane depolarization (Fog et al., 2006; Moron et al., 2003; Richardson et al., 2016). Collectively, these effects of AMPHs on DAT activity result in a robust increase in extracellular DA levels that contribute to the highly addictive properties of the drug.

Other Mechanisms

In addition to DAT-mediated increases in extracellular DA through disrupting DAT activity, METH also decreases the activity of monoamine oxidase, resulting in decreased dopamine metabolism and thus prolonged elevated extracellular DA levels (Sulzer et al., 2005). Importantly, METH also affects others neurotransmitter systems outside of the monoamines. ATSs have been shown to activate the endogenous opioid system, also contributing to the rewarding effects of the drugs (Chiu et al., 2005; Jones and Holtzman, 1994; Shen et al., 2010). Additionally, studies have demonstrated that METH increases levels of glutamate, acetylcholine, and the neuropeptide neurotensin (Courtney and Ray, 2014).

Chronic Effects on the Dopaminergic System

High doses and persistent use of METH can lead to neurotoxic effects on dopaminergic neurons. Human positron emission tomography (PET) imaging in METH abusers demonstrates decreases in striatal DAT density, D_2 dopamine receptor (D_2R) availability, and VMAT-2 density compared to non-METH users (Johanson et al., 2006; McCann et al., 1998; Volkow et al., 2001a; Volkow et al., 2001c). The mechanisms by which these dopaminergic markers are down-regulated are not understood, however evidence suggests that METH-mediated oxidative stress may be responsible for neuronal toxicity (Berman et al., 2008). Interestingly, human imaging studies have revealed that prolonged METH abstinence (more than one year) can improve these deficits in dopaminergic markers (Curtin et al., 2015; Volkow et al., 2001b). Despite the potential for improvement after abstinence, the connection between METH use and Parkinson’s disease (PD) is an ongoing concern. Individuals with a history of METH use were reported to have nearly a three-fold increased risk for developing PD (Callaghan et al., 2010; Callaghan et al., 2012), however whether or not METH use directly causes PD remains unresolved (Guilarte, 2001; Kish et al., 2017).

Treatment Strategies

Currently, there are few effective options for the treatment for METH addiction. Psychosocial interventions are often employed consisting of either Cognitive-Behavioral Treatment (CBT) or Contingency Management (CM) (Courtney and Ray, 2014). CBT involves teaching individuals how to reduce or discontinue drug use, whereas CM involves using positive reinforcement, such as money vouchers, to promote decreased drug use (Lee and Rawson, 2008). Unfortunately, these psychosocial treatments have low rates of treatment induction as well as patient retention (Shearer, 2007). Currently, there is no FDA-approved drug treatment for METH addiction, but several drugs are currently under clinical trial. These drugs mainly target dopaminergic, serotonergic, GABAergic, and/or glutamatergic systems in the brain (Courtney and Ray, 2014). In addition to these known pathways involved in psychostimulant addiction, there is growing interest in a unique target in the brain for the treatment of METH addiction called the sigma-1 receptor (σ_1R), which will be the focus for the remainder of this review.

3. SIGMA-1 RECEPTOR

The sigma-1 receptor (σ_1R) is a ubiquitously expressed protein implicated for the treatment of a number of neurological conditions including stroke, neurodegenerative disease, psychiatric disorders, and neuropathic pain (Rousseaux and Greene, 2015). The σ_1R is widely expressed throughout the central nervous system and peripheral organs. Within the brain, σ_1Rs are highly concentrated within the limbic system and brainstem (Maurice et al., 2002). At the cellular level, the σ_1R is located at the endoplasmic reticulum (ER) membrane where it possesses chaperone activity in response to misfolded proteins. A unique property of this chaperone, however, is that it can also be regulated by different ligands in an agonist-antagonist manner. Upon activation, the σ_1R acts as intracellular signaling modulator, regulating a variety of cellular functions. Despite the σ_1R's wide expression and numerous functions, σ_1R knockout mice are viable and do not display any overt phenotype. In part, this could be due to compensatory mechanisms occurring during development. Interestingly, a depressive-like phenotype has been observed in σ_1R knockout mice, supporting a role for σ_1Rs in psychiatric disease (Rousseaux and Greene, 2015; Sabino et al., 2009). Although there are many unanswered mechanistic questions, the past 20 years of research suggests that the σ_1R is a viable target for the treatment of numerous pathological conditions.

Protein Characterization

Because of their affinity for the opioid-receptor targeting benzomorphan N-allylnormetazocine (SKF-10,047), sigma receptors (σR) were initially classified as the "σ opioid" receptor subtype in 1976 (Martin et al., 1976). A later study revealed that the classic opioid receptor antagonist naltrexone failed to antagonize the effects of SKF-10,047, leading researchers to distinguish the σR as a non-opioid receptor (Vaupel, 1983). SKF-10,047 was later shown to have a similar behavioral profile as the dissociative drug phencyclidine (PCP) as well as share binding to the N-methyl-D-aspartate (NMDA) receptor, creating further uncertainty about the σR's identity (Hayashi and Su, 2004; Quirion et al., 1992). Eventually, the development of more selective ligands revealing a distinct binding profile led to the recognition of σRs as a separate class of proteins (de Costa et al., 1989).

At least two subtypes of σRs have been identified, sigma-1 (σ_1) and sigma-2 (σ_2), initially characterized based on their differential ligand affinities (Maurice et al., 2002; Quirion et al., 1992). In general, σ_1Rs have higher affinity and stereoselectivity for (+)-isomers of benzomorphans whereas σ_2Rs have more affinity for (−)isomers (Hellewell et al., 1994). Additionally, the subtypes display different molecular weights; the σ_1R is identified at 25–30 kDa and the σ_2R at 18–21 kDa (Maurice et al., 2002). The σ_1R was first cloned from guinea pigs in 1996 (Hanner et al., 1996) and later identified as a 223-amino acid protein with 90% homology across mammalian species (Su et al., 2010). Interestingly, the σ_1R has 33% identity and 66% homology with a yeast sterol C8-C7 isomerase involved in sterol biosynthesis (Hanner et al., 1996; Su and Hayashi, 2003). Although the σ_1R was later shown to bind cholesterol and to be involved in subcellular lipid distribution (Hayashi and Su, 2005; Palmer et al., 2007), it lacks sterol or cholesterol isomerase activity (Labit-Le Bouteiller et al., 1998). Furthermore, the σ_1R lacks enzymatic activity and shares no sequence homology with any other known mammalian proteins (Hayashi and Su, 2003b; Su et al., 2010), further complicating efforts to categorize the protein. In 2016, the crystal structure of the human σ_1R was identified and shown to have a trimeric organization with a single transmembrane domain for each protomer (Schmidt et al., 2016). Because of these advances in characterizing the σ_1R, the σ_1R has been more widely investigated throughout the field compared to the σ_2R. Only recently was the σ_2R cloned and identified as TMEM97 (Alon et al., 2017), an ER membrane protein known to contribute to cholesterol homeostasis (Alonso et al., 2000; Bartz et al., 2009) and potentially other cellular functions (Derbez et al., 2002; Sahn et al., 2017; Walker et al., 1993). It is unclear how this recent development might alter the interpretation of previous σ_2R studies. It should be noted that although several of the σR ligands discussed in this report and used in many other studies have affinity for both the σ_1R and σ_2R, the focus of this review is on σ_1Rs. This is important to consider as the two subtypes may differ in cellular activity and thus overall function.

Pharmacology

A variety of drugs bind to σ_1Rs, including benzomorphans and PCP as described above. Although there is no known explicit endogenous ligand, neurosteroids including progesterone and dehydroepianderosterone (DHEA) have affinity for the σ_1R (Su et al., 1988a). Additionally, N,N-dimethyltryptamine (DMT), an endogenous compound also used recreationally as a hallucinogen, has been shown to bind to the σ_1R (Fontanilla et al., 2009). DMT is generally recognized as targeting serotonin receptors, but DMT's affinity for the σ_1R suggests a potential role for σ_1Rs in its psychedelic effects and further implicates the σ_1R in psychiatric disease (Rousseaux and Greene, 2015).

In addition to these compounds, a wide range of unrelated and structurally diverse ligands used both recreationally and therapeutically in humans have high affinity for the σ_1R. This includes the drugs of abuse cocaine (Sharkey et al., 1988) and METH (Nguyen et al., 2005), the antipsychotic drug haloperidol (Su, 1982), and antidepressants such as fluoxetine (Prozac®) (Safrany and Brimson, 2016) and sertraline (Zoloft®) (Narita et al., 1996). Importantly, fluoxetine has been reported to reach serum concentrations at clinically relevant doses that can bind σ_1Rs (Di Rosso et al., 2016; Safrany and Brimson, 2016), thus the actions of these drugs and potentially many other clinically used drugs could be in part due

to their interactions with the σ_1R. Additionally, anticonvulsants, cytochrome P450 inhibitors, and monoamine oxidase inhibitors also have reported σ_1R affinity (Maurice et al., 2002). It is still unclear if and how the σ_1R contributes to the actions of many of these drugs, but these findings have generated great interest in the potential clinical role of the σ_1R and has also led to the generation of several novel drugs selectively targeting σ_1Rs. Table 1 summarizes drugs mentioned in this review with their affinities for σ_1R, σ_1R, and DAT.

Defining σ_1R ligands as agonists or antagonists has been complicated for various reasons. Several ligands with σ_1R affinity remain uncharacterized as either agonists or antagonists (Gonzalez-Alvear and Werling, 1994). One widely accepted metric for determining σ_1R agonist activity is the ability of the ligand to dissociate the σ_1R from its constitutive binding partner protein, Binding immunoglobulin Protein (BiP). Agonists dissociate σ_1R from BiP whereas antagonists either increase the association or block the effect of agonists (Hayashi and Su, 2007). Interestingly, several selective σ_1R ligands show no effect when administered alone and only modulate stimulated cellular responses (Hayashi and Su, 2003a), limiting the feasibility of classifying ligands as agonists versus antagonists based cellular effects. Additionally, modulation of these responses is often dose-dependent as a number of studies have shown opposing effects depending on whether high or low doses were used (Rousseaux and Greene, 2015); this makes it challenging to compare diverse studies using different doses of the same σ_1R ligands. Another proposed method of determining agonist versus antagonist activity is that σ_1R agonists mimic the effects of σ_1R overexpression while σ_1R antagonists mimic σ_1R knockdown (Mei and Pasternak, 2002), although this requires further validation. Additionally, the possibility that some σ_1R antagonists may act as partial or inverse agonists is a developing concept within the field. It is important to consider that many σ ligands to-date have dual or partial affinity for both σ receptor subtypes making it difficult to distinguish which target is primarily contributing to the effects of the drugs. Furthermore, ligands may act as an agonist of one subtype but an antagonist of the other, and the cellular responses to agonism and antagonism of the σ_2R are not defined. Adding additional complexity, it was recently shown that drugs thought to be highly selective for the σ_1R can also directly influence the activity of voltage-gated K^+ channels, potentially explaining the effects on neuronal physiology without a direct role of the σ_1R (Liu et al., 2017). Lastly, the *in vitro* pharmacokinetics of many of these selective σR ligands is undetermined, with the half-life and brain concentrations of these drugs after administration unknown. Given this complexity, further investigation is required to properly characterize and categorize σR ligands and allow for proper interpretation across studies utilizing these drugs.

Cellular Localization

The cellular localization of the σ_1R is dynamic in nature. σ_1Rs exist predominantly in the endoplasmic reticulum (ER) membrane (Hayashi et al., 2000) where they are highly localized in cholesterol-rich areas of the ER adjacent to the mitochondria called the mitochondrial-associated membrane (MAM). Additionally, σ_1Rs have also been localized to the plasma membrane, nuclear envelope, and post-synaptic thickenings of neurons (Alonso et al., 2000; Su et al., 2010). As described above, the σ_1R is constitutively bound to BiP, and agonists dissociate σ_1R from BiP allowing σ_1R translocation within the cell. In addition to

agonist activation, ER Ca^{2+} depletion has also been shown to dissociate the σ_1R from BiP, suggesting a role of the σ_1R as a sensor of ER Ca^{2+} levels (Hayashi and Su, 2007). A recent study showed that mutations in the σ_1R gene linked to neurodegenerative diseases resulted in aberrant cellular localization of the σ_1R, supporting the importance of proper σ_1R localization in its physiological function (Wong et al., 2016).

While the precise localization of σ_1Rs is poorly understood, multiple independent studies have demonstrated that σ_1Rs exist within or adjacent to the plasma membrane. Subcellular fractionation in rat brain homogenates revealed (+)[^{3}H]SKF-10,047 binding sites within non-synaptic plasma membrane fractions (Hayashi and Su, 2003a; McCann and Su, 1990). Treatment with selective σ_1R ligands increased the detection of σ_1Rs in the plasma membrane fraction using this method, supporting the hypothesis that σ_1R activation promotes its translocation from the ER to other cellular compartments such as the membrane (Hayashi et al., 2000). A 2013 study by Kourrich et al. suggested that the σ_1R is directly incorporated within the plasma membrane via an assay detecting C- and N- terminal tags on the σ_1R putatively at the membrane (Kourrich et al., 2013). In contrast, Mavlyutov et al. used electron microscopy in motor neurons as well as ganglion cells to identify σ_1R localization to subsurface cisternae of the ER near but not integral to the plasma membrane (Mavlyutov et al., 2015; Mavlyutov et al., 2010). These ER subsurface cisternae, also referred to as cortical ER, are areas of the ER that come in close contact with the plasma membrane and provide direct communication between ER and membrane proteins (Berridge, 1998; Kosaka, 1980; Rosenbluth, 1962; Spacek and Harris, 1997). Importantly, the σ_1R has been shown to interact with and modulate the activity of various membrane proteins (Pabba, 2013; Rousseaux and Greene, 2015), supporting the notion that a population of σ_1Rs are capable of translocating to the area at or near the plasma membrane where they can directly or indirectly modulate the activity of transmembrane proteins.

Cellular Functions

σRs regulate a variety of second messenger signaling pathways, including cyclic guanosine monophosphate (cGMP), inositol phosphates, kinases, and Ca^{2+} (Matsumoto et al., 2003). σ_1Rs modulate these effects in a manner distinct from traditional ionotropic or metabotropic receptors by translocating between cellular compartments. Figure 2 broadly summarizes the existing theories for the cellular function of σ_1R. Overall, the σ_1R is considered pro-survival under cellular stress (Hayashi and Su, 2007; Pabba et al., 2014). As an ER chaperone protein, it attenuates protein misfolding and stabilizes other ER proteins (Hayashi and Su, 2007). σ_1R interactions with the IP_3R type 3 at the MAM have been well characterized and are hypothesized to regulate IP_3R-mediated Ca^{2+} mobilization from the ER to the mitochondria. This in turn promotes cell survival by upregulating Ca^{2+}-dependent enzymes involved in the tricarboxylic acid (TCA) cycle (Hajnoczky et al., 1995; Hayashi and Su, 2007). Thus, by promoting cellular metabolism, the σ_1R is believed to promote cell survival.

Numerous reports indicate that the σ_1R also regulates Ca^{2+} homeostasis outside of the MAM. A study utilizing different chemical classes of selective σ_1R agonists, pregnenolone sulfate, (+)-pentazocine, and PRE-084, revealed no effect of these drugs alone but reported a potentiation of bradykinin-induced Ca^{2+} release from the ER. Interestingly, the different σ_1R

agonists differentially affected depolarization-induced Ca^{2+} increases, with PRE-084 potentiating the response and pregnenolone sulfate and (+)-pentazocine attenuating it (Hayashi et al., 2000). This study highlights a number of important concepts within σ_1R biology, namely the modulatory nature of selective σ_1R ligands (i.e. the lack of effect when administered in the absence of a stimulated response), the different modulatory responses of the different σ_1R ligands despite all drugs used being classified as σ_1R agonists, and the ability of σ_1Rs to regulate both ER Ca^{2+} release as well as extracellular Ca^{2+} influx supporting diversity of cellular functions. The latter is supported by reports showing σ_1R-regulation of L-type Ca^{2+} channel activity in hippocampal slices as well as retinal ganglion cells (Sabeti et al., 2007; Tchedre et al., 2008). Additionally, σ_1R ligands were reported to differentially influence both NMDA receptor and nicotinic acetylcholine receptor mediated Ca^{2+} signaling (Hayashi et al., 1995; Paul et al., 1993). More recently, activation of the σ_1R was shown to inhibit store operated Ca^{2+} entry (SOCE), a ubiquitously expressed pathway that facilitates Ca^{2+} influx into the cell in response to ER Ca^{2+} depletion (Srivats et al., 2016). This attenuation by the σ_1R was proposed to prevent excess Ca^{2+} influx that may in turn lead to apoptosis. Overall, these studies suggest that the σ_1R can influence multiple intracellular Ca^{2+} signaling pathways through a variety of mechanisms, potentially acting in parallel.

Protein Interactions

The σ_1R associates with and regulates the activity of diverse classes of proteins both intracellularly and at the plasma membrane. This includes several different voltage-gated ion channels (VGICs) where interactions with these channels can have either inhibitory or enhancing effects on channel activity (Kourrich et al., 2012; Pabba, 2013). Some examples include σ_1R associations with the Kv1.4 channel in posterior pituitary of rats (Aydar et al., 2002), L-type Ca^{2+} channels in retinal ganglion cells (Tchedre et al., 2008), Kv1.3 in a human embryonic kidney cell (HEK) line (Kinoshita et al., 2012), and Kv1.2 channels in medium spiny neurons of nucleus accumbens (Kourrich et al., 2013). Interactions between the σ_1R and different ion channels, particularly K^+ channels, support the hypothesis that the σ_1R may act as a regulatory subunit for these channels (Aydar et al., 2002) and implicates the σ_1R as an indirect regulatory of neuronal excitability.

In addition to VGICs, the σ_1R has also been shown to interact with and modulate the activity of the NMDA receptor in the rat hippocampus (Balasuriya et al., 2013; Pabba et al., 2014) as well as the μ opioid receptor expressed in HEK cells (Kim et al., 2010). In addition to interactions with BiP, IP_3R, and STIM1 described above, the σ_1R forms a complex with other ER-localized proteins including ankyrin B. σ_1R agonist treatment dissociated ankyrin from the IP_3R, potentiating IP_3-mediated intracellular Ca^{2+} signaling (Hayashi and Su, 2001). The σ_1R also associates with one of the ER stress-sensing proteins involved in the unfolded protein response, inositol-requiring enzyme 1 (IRE1). Mori et al. found that like the σ_1R, IRE1 is also enriched at the mitochondrial-associated membrane, and σ_1R stabilizes IRE1 thereby prevent its degradation under cellular stress (Mori et al., 2013).

Relevant to its potential role in psychostimulant addition, the σ_1R also associates with proteins directly involved in dopaminergic signaling. This includes the D_1R in HEK cells co-

expressing σ_1R/D_1R, where researchers reported that σ_1R ligands attenuated cocaine-induced D_1R-mediated increases in cAMP levels and ERK1/2 phosphorylation in cells as well as striatal tissue (Navarro et al., 2010). The same group later found that the σ_1R interacts with the D_2R, and cocaine binding to this complex inhibits downstream D_2R-mediated signaling pathways (Navarro et al., 2013). More recently, the σ_1R/DAT association was revealed in HEK cells co-expressing σ_1R/DAT (Hong et al., 2017b). This association was shown to increase DA uptake at high concentration of σ_1R agonist and enhanced cocaine binding to the transporter. In an independent study, our laboratory also confirmed that the σ_1R associates with DAT at or near the plasma membrane and that this association is potentiated by combined treatment with a σ_1R agonist and METH (Sambo et al., 2017). This study is further described in a later section of the review. Overall, σ_1R interactions with D_1R, D_2R, and DAT provide further support for the role of σ_1R in modulating the dopaminergic neurotransmission and the effects of psychostimulants and also provide potential molecular mechanisms by which the σ_1R mediates its effects.

4. SIGMA-1 RECEPTOR AND THE DOPAMINERGIC SYSTEM

The role of σRs in dopaminergic neurotransmission has been of interest since early findings that antipsychotics and other drugs involved in dopaminergic signaling have affinity for σRs (Iyengar et al., 1990; Wachtel and White, 1988). σRs are expressed in dopaminergic regions including the striatum, substantia nigra (SN), and ventral tegmental area (VTA) (Gundlach et al., 1986; Hayashi et al., 2010; McLean and Weber, 1988). Using immunohistochemistry, σ_1Rs were identified in dopaminergic neurons (Francardo et al., 2014). Despite several reports, well-defined functional implications of σRs in the regulation of dopamine neurotransmission remain unclear.

Effects on Dopamine Release

Reports on the effects of σRs on DA release have yielded varying results over the past several years. In 1990, Iyengar et al. first investigated the effect of σR ligands on DA release in the striatum and olfactory tubercles and found that local administration of the benzomorphan σR agonists (+)-pentazocine and (+)-SKF 10,047 increased the levels of DA metabolites dihydrophenylacetic acid (DOPAC) and homovanillic acid (HVA) with no change in DA steady state levels (Iyengar et al., 1990). Benzomorphans (+)-*N*-allylnormetazocine and (+)-pentazocine were later shown to increase the activity of tyrosine hydroxylase, the rate limiting enzyme for DA synthesis, in *ex vivo* rat striatal tissue (Booth and Baldessarini, 1991). While this implied a role for σRs in DA metabolism and synthesis, there was no distinction between the effect of σ_1R and σ_2R because the antagonist used to block these effects, BMY-14802, is not selective between the two subtypes. In 1993, Patrick et al. showed that systemic administration of σR agonists (+)-pentazocine and 1,3-Di-(2-tolyl)guanidine (DTG) increased striatal DA levels in freely moving rats. In this study, only higher doses of the σ_1R selective ligand (+)-pentazocine had an effect whereas lower doses of the non-discriminant $\sigma_{1/2}$R agonist DTG were sufficient to increase DA levels. This suggested that activation of the σ_2R, rather than the σ_1R, induced DA release in these rats (Patrick et al., 1993). This conclusion was further substantiated in later studies revealing systemic injection of only higher doses of (+)-pentazocine increased striatal DA levels

(Gudelsky, 1995) and intra-nigral injections of $\sigma_{1/2}$R agonist DTG increased extracellular levels of dopamine metabolites DOPAC and HVA in the striatum (Bastianetto et al., 1995). The effect of σR ligands on DA release was later shown to be biphasic in a study where intra-striatal administration of (+)-pentazocine, (−)-pentazocine, or DTG all initially increased DA levels followed by a prolonged decrease (Gudelsky, 1999). Supporting the inhibitory effect of σR on DA release, intra-striatal application of the $\sigma_{1/2}$R agonist MR200 as well as DTG decreased DA levels in the striatum (Moison et al., 2003).

Later efforts to clarify the role of the σR subtype on DA release were made possible with the development of more selective σ_1R ligands. In 1997, Kobayashi et al., showed that acute oral administration of the selective σ_1R agonist SA4503 increased DA levels in the rat frontal cortex, but interestingly not the striatum or midbrain (Kobayashi et al., 1997). This was further supported by a more recent study showing a range of doses of SA4503 as well as the σ_1R antagonists BD1047 and BD1063 failed to evoke [^{3}H]DA overflow in preloaded rat striatal slices (Rodvelt et al., 2011a), however the frontal cortex was not examined in this report. In 2011, Garcés-Ramírez et al. recapitulated the dose-dependent effects of σR ligands demonstrating again that DTG increased dopamine levels in the nucleus accumbens at lower concentrations whereas the selective σ_1R agonist PRE-084 only increased dopamine levels at higher doses. Furthermore, the PRE-084-mediated increase in dopamine levels was not blocked by σ_1R antagonists BD1063, suggesting potential off-target effects PRE-084 at the dose used in this study (Garces-Ramirez et al., 2011). PRE-084 was later tested at 1, 3.2, and 10 mg/kg and shown to have no effect on extracellular DA levels in the nucleus accumbens shell in saline-treated animals as well as animals with a history of cocaine exposure (Hiranita et al., 2013a).

Taken together, these studies suggest that σ_2R activation, but not σ_1R activation, may regulate DA neurotransmission within the striatum. The potential role of σ_1R in cortical DA neurotransmission was observed in at least one report, suggesting potential brain region differences in the actions of σRs. Furthermore, the time-dependency of these effects may also contribute to whether potentiation or inhibition of DA release is observed. The mechanisms by which the σRs promote dopamine release are currently unknown, although (+)-pentazocine-mediated dopamine release in the striatum was shown to occur in a DAT-independent manner (Gudelsky, 1995). Additionally, treatment with the σ_1R agonist (+)-pentazocine increased tyrosine hydroxylase activity (Booth and Baldessarini, 1991) and the σ_1R agonist SA4503 increased in L-DOPA levels in the presence of DOPA decarboxylase inhibitors (Kobayashi et al., 1997), suggesting a role of σRs in increasing DA synthesis. Currently, the molecular mechanisms by which σR ligands promote DA release or synthesis are unknown.

Electrophysiological Effects on Dopamine Neurons

In addition to dopamine release, the effects of σR ligands on the firing activity of dopaminergic neurons has also been examined. Dopaminergic neurons display spontaneous baseline firing activity (Grace and Bunney, 1984). Consistent with its ability to increase locomotor activity alone, the σ_1R agonist (+)SKF-10,047 also increased the basal firing activity of VTA DA neurons which was blocked by the σ_1R antagonist rimcazole (Ceci et

al., 1988). Proposed as a potential antipsychotic drug, the $\sigma_{1/2}$R antagonist BMY 14802 reversed the effect of apomorphine (a D_2R agonist) on inhibiting the firing activity of SN and VTA dopaminergic neurons (Wachtel and White, 1988). *In vivo* extracellular recordings in the SN revealed intravenous administration of the $\sigma_{1/2}$R agonist (+)-3-PPP decreased neuronal firing rate which was reversed by treatment with BMY 14802 (Steinfels and Tam, 1989). These early studies suggest a role for the σR in dopaminergic neuron firing activity or D_2R-mediated inhibition of firing activity, however relatively non-specific ligands were utilized. *In vivo* recordings in the SN and VTA dopaminergic neurons of rats intravenously injected with the selective σ_1R agonist SA4503 showed no change on the spontaneous firing activity but significantly decreased the number of spontaneously active neurons in the SN and increased the number of spontaneously active neurons in the VTA (Minabe et al., 1999). Further studies are required to more conclusively determine the role of the σ_1R in the firing activity of dopamine neurons. Additionally, the mechanisms involved in this regulation are not characterized, but σ_1R associations with different ion channels may serve as potential mechanisms that have yet to be investigated.

Role in Parkinson's Disease

The established role of the σ_1Rs in dopaminergic physiology has also led to the investigation of the therapeutic potential of the σ_1R in Parkinson's disease (PD). Human PET imaging revealed lower binding of a radiolabeled σ_1R tracer ([^{11}C]SA4503) on the side of the anterior putamen that exhibited lower radiolabeled DAT substrate binding (Mishina et al., 2005). While this meant that the σ_1R could be a plausible marker of dopaminergic degeneration, there was no difference in the binding measured between PD patients and controls, ruling out any potential of σ_1R imaging as a biomarker for early PD.

Studies in animal models reported paradoxical results in regard to the role of σ_1R as a neuroprotective target. In 6-hydroxydopamine (6-OHDA) lesioned mice, five weeks of treatment with the σ_1R agonist PRE-084 (0.3 mg/kg) produced a profound recovery of motor function as well as DA neuronal protection (Francardo et al., 2014). The treatment also increased levels of BDNF, GDNF, and pERK and decreased microglial activation. In an alternative model utilizing the neurotoxin MPTP, σ_1R hetero- and homozygous knockout mice had reduced DA cell loss and recovery of motor function subsequent to MPTP injection (Hong et al., 2015). This effect was attributed to σ_1R deficiency induced suppression of NMDA receptors. The observed neuroprotective σ_1R knockout effect was recapitulated in wild-type mice using the σ_1R antagonist NE-100. Further complicating these paradoxical findings, the σ_1R knockout mouse was shown to undergo age-dependent dopaminergic neurodegeneration, suggesting that the σ_1R knockout mouse may be suitable to serve as a unique animal model of PD (Hong et al., 2017a). The aged σ_1R KO mice exhibited multiple pathological characteristics that mimic the hypothesized cascade leading to cell death in PD, and also exhibited measurable motor defects. Taken together, these studies underscore the complexity of the σ_1R's role in neuronal function and disease, yet still provide rationale for the therapeutic targeting of the σ_1R in PD.

5. SIGMA-1 RECEPTOR AND METHAMPHETAMINE

Interest in the role of σRs in METH addiction stems from the early observation that the σR agonist (+)SKF-10,047 induces psychotomimetic effects in dogs (Martin et al., 1976). Additionally, the discovery that antipsychotics such as haloperidol have high affinity for the σ_1R and the known parallels between schizophrenia and METH-induced psychosis further provoked the investigation of the potential role of σRs in psychostimulant addiction. At least one Japanese study found no link between known mutations in the σ_1R gene and METH abuse, concluding that σ_1Rs are unlikely to play a major role in the susceptibility for METH addiction (Inada et al., 2004). Although no genetic link was observed in humans, a number of studies have revealed restorative effects of σR ligands in animal models of METH addiction. It should be noted that the effects of σR ligands have also been widely studied in models of cocaine addiction. Although both METH and cocaine are widely abused psychostimulants, the different cellular mechanisms, pharmacokinetics, and potential long-term effects are worth considering these two drugs of abuse as distinct addiction targets. This is briefly discussed in the Conclusions section.

Regulation of Sigma-1 Receptor Expression

The upregulation of σ_1R expression after METH administration was first demonstrated in 1993 in rats exposed to 4 mg/kg of METH for 10 days. Increased binding of [^{3}H](+)-pentazocine was observed in the SN, frontal cortex, and cerebellum, suggesting a upregulation of σ_1Rs in response to METH (Itzhak, 1993). In 2004, Stefanski et al. investigated the effect of both self-administration and passive administration of METH on σ_1R levels in the brain (Stefanski et al., 2004). An increase in σ_1R protein levels, as measured via Western blot, was found in the midbrain of rats self-administering METH 5-days-per-week for 5 weeks but not in rats that passively received the same amount of METH over the same period (Stefanski et al., 2004). In 2009, Hayashi et al. similarly investigated the effect of METH administration on σ_1R levels, as well as other chaperone proteins, in the brain of rats either self-administered METH or passively received the drug. They found via Western blot that ER chaperone proteins σ_1R, BiP, and calreticulin were all significantly elevated in the VTA and SN of rats under both treatment paradigms (Hayashi et al., 2010). This is consistent with studies reporting ER chaperone protein upregulation by METH due to ER stress (Jayanthi et al., 2004). The differences between the Stefanski study where σ_1R levels were only upregulated in the midbrain of self-administering rats compared to the Hayashi study where the σ_1R was upregulated in the VTA and SN of both rats self-administering and passively receiving METH was attributed to the detection of proteins in the VTA and SN as opposed to the entire midbrain. Because a global upregulation of σ_1R levels in many different brain regions was not observed, this upregulation appears to selectively occur in dopaminergic structures. Currently, the functional consequence of the upregulation of σ_1R levels in response to METH is unknown. σ_1R upregulation may be a contributing factor to the development of METH addiction, or conversely could act as a compensatory mechanism to counteract the untoward effects of METH.

Interactions with the Sigma-1 Receptor

In addition to METH-induced increases in σ_1R levels in the rodent VTA and SN, METH interacts with the σ_1R at physiologically relevant concentrations. METH's affinity for σRs was first demonstrated in 1993 in whole rat brain membrane preparations showing a concentration-dependent inhibition of [^{3}H](+)-pentazocine binding by METH (Itzhak, 1993). In 2005, Nguyen et al. determined the binding affinity of METH for the σ_1R and σ_2R in rat brains labeled with [^{3}H](+)-pentazocine for σ_1R selectivity or [^{3}H]DTG in the presence of (+)-pentazocine for σ_2R selectivity. METH displayed over 20-fold selectivity for the σ_1R over the σ_2R (K_i 2.16 ± 0.25 μM vs. 46.67 ± 10.34 μM, respectively) (Nguyen et al., 2005). The consequences of METH binding to the σ_1R are currently unknown; however, Hayashi et al. demonstrated that METH treatment increased the association between the σ_1R and BiP suggesting METH may have antagonist activity (Hayashi and Su, 2007). A recent review by Yasui and Su posits that METH may act as an inverse agonist (Yasui and Su, 2016). In addition to METH, both cocaine and MDMA also have affinity for the σ_1R (Brammer et al., 2006; Matsumoto et al., 2002; Sharkey et al., 1988).

Locomotor Activity

Before σRs were identified as a unique class of proteins in the brain, the "σ opioid receptor" agonist (+)SKF-10,047 was shown to induce psychotomimetic effects alone (Fujiwara et al., 1990; Martin et al., 1976). This finding, in addition to studies described above suggesting a role of σRs in the regulation of dopamine homeostasis, predicted early on a potential role of σRs in basal locomotion as well as METH-stimulated locomotor activity. Although (+)SKF-10,047, as well as pentazocine, promote hyperactivity, more selective σ_1R ligands do not induce locomotion when administered alone. When investigating the effects of METH-induced (3 mg/kg) acute locomotor activity in σ_1R knockout mice, no difference was observed between the knockout and wild-type mice (Fontanilla et al., 2009). The lack of effect of selective σ_1R ligands alone as well as METH-stimulated locomotor activity being unaffected in σ_1R knockout mice suggests that the σ_1R is not required to regulate motor activity at baseline or in response to METH. In 1992, Ujike et al. showed that while the nonselective $\sigma_{1/2}$R antagonist BMY 14802 had no effect on acute METH-induced (2 mg/kg) locomotor activity, it blocked locomotor sensitization after repeated METH exposure (Ujike et al., 1992a). Similarly, the selective σ_1R ligand MS-377 also attenuated the development of METH-induced (2 mg/kg) locomotor sensitization; however, it was not distinguished whether MS-377 acted as a σ_1R agonist or antagonist in this study (Takahashi et al., 2000). In the same report that determined the affinity of METH for the σRs, treatment with σ_1R antagonists BD1063 and BD1047 as well as administration of an antisense oligodeoxynucleotide against the σ_1R into the ventricles of rats attenuated acute METH-induced locomotor activity at METH doses between 0.1 and 3 mg/kg (Nguyen et al., 2005). The nonselective $\sigma_{1/2}$R antagonist AC927 also decreased acute locomotor activity induced by 0.5 and 1 mg/kg METH in a separate study (Matsumoto et al., 2008). Both intraperitoneal injection and oral administration of the $\sigma_{1/2}$R ligand AZ66, which putatively acts as an $\sigma_{1/2}$R antagonist, dose-dependently decreased METH-induced (1 mg/kg) acute locomotor activity as well as METH-induced locomotor sensitization (Seminerio et al., 2012). It is currently unclear why some σR antagonists attenuate acute locomotor activity and some are

only effective on locomotor sensitization; nevertheless, these findings suggest specific σR antagonists may have different effects.

In addition to σR antagonists and knockdown, the effect of σ_1R agonists on METH-induced locomotion is investigated. Administration of the selective σ_1R agonist SA4503 dose dependently affected METH-induced (0.5 mg/kg) locomotor activity with lower doses enhancing hyperactivity and higher doses inhibiting it (Rodvelt et al., 2011b). More recently, Miller et al., 2016 investigated the effect of different N-phenylpropyl-N′-substituted piperazine ligands, including SA4503, on METH-induced hyperactivity (Miller et al., 2016). All ligands tested had high affinity for the σ_1R and no appreciable affinity for DAT. They found that higher doses of the compounds attenuated METH-induced (0.5 mg/kg) locomotor activity, whereas lower doses potentiated it (Miller et al., 2016). Utilizing a different selective σ_1R agonist, our laboratory recently revealed that 8 mg/kg PRE-084 attenuates acute METH-stimulated (2 mg/kg) locomotor activity. Interestingly, 30 mg/kg of the σ_1R antagonist BD1063, but not 10 mg/kg, also significantly reduced METH-induced locomotor activity. When analyzing locomotion during the pretreatment period, we found that 30 mg/kg BD1063 *alone* decreased locomotion, an effect that appears to be acute as no difference was detected after a subsequent one hour of saline treatment. This effect of 30 mg/kg of BD1063 on locomotor activity alone suggests this dose of the antagonist may have some sedative effects (Sambo et al., 2017). Collectively, these reports indicate that the type and dose of σ_1R ligand used may present varying results but support the potential ability of σ_1R ligands to reduce the hyperactive effects of METH, both acutely and after sensitization. A comprehensive study using multiple σR ligands at different doses would potentially provide a clearer picture of how σR ligands influence METH-stimulated locomotion.

Stereotypic Behavior

Another behavioral consequence of METH exposure is the induction of repetitive and compulsive behaviors called stereotypies (Canales and Graybiel, 2000). In rodents, this includes repetitive grooming, sniffing, biting, licking, head-bobbing, and circling (Kitanaka et al., 2009). An early study by Ujike et al. showed that treatment with 3 mg/kg of the $\sigma_{1/2}$R agonist (+)-3-PPP acutely decreased rearing, locomotion, sniffing, and head movement but potentiated these behaviors when higher doses were utilized. In rats that received repeated 4 mg/kg METH treatment followed by 5 to 8 days of abstinence, (+)-3-PPP enhanced sensitization to locomotor behavior but decreased sensitization to rearing, sniffing, and head movement (Ujike et al., 1992b). Similar to this study, the $\sigma_{1/2}$R antagonist BMY 14802 also had no effect on acute stereotypic behavior but decreased stereotypy sensitization (Akiyama et al., 1994). While MS-377 did not affect acute METH-induced stereotypic behavior in rats, pretreatment significantly attenuated the behavioral sensitization of stereotypic behavior in rats receiving METH for 10 days (Takahashi et al., 2000). Investigating the effect of different σR ligands with dual affinity as well as selective affinity for σ_1R and σ_2R, Kitanaka et al. found that different σR ligands differentially affected the pattern and the type of stereotypies expressed but produced no change in the overall frequency of METH-induced stereotypy behavior (Kitanaka et al., 2009). While many of these studies only reported effects on stereotypy sensitization and not acute stereotypic behavior, several of the

METH locomotor studies showed acute effects of σ_1R ligands, this suggesting the potential involvement of different mechanisms across different METH-induced behaviors.

Reinforcing Behavior

In addition to the acute behavioral effects of psychomotor activation and stereotypy behavior, the role of σ_1R in animal models of addictive-like behavior has also been investigated. While the σ_1R agonist SA4503 did not substitute for METH at any dose tested, pretreatment with SA4503 augmented drug discrimination for METH such that lower dose of METH elicited responding compared to animals pretreated with saline (Rodvelt et al., 2011b). In contrast, in 2013 Rahmadi et al. found that the antidepressant and σ_1R agonist fluoxetine decreases the rewarding effects of METH as measured by conditioned place preference (CPP). The effect of fluoxetine was blocked by the σ_1R antagonist NE-100, suggesting the role of σ_1Rs in attenuating METH-induced reinforcing behaviors (Rahmadi et al., 2013). Similar to this study, in 2014 Mori et al. reported that the σ_1R agonist SA4503 but not (+)-pentazocine reduced CPP to morphine, cocaine, and METH (Mori et al., 2014). This study supports the ability of the σ_1R agonist SA4503 to attenuate the rewarding effects of drugs of abuse in general and highlights the phenomenon that not all σ_1R agonists produce the same outcomes. Similar to SA4503, the σ_1R agonist PRE-084 also reduced the acquisition of METH-induced CPP in rodents (Sambo et al., 2017). Considering fluoxetine, SA4503, and PRE-084 are all more selective for the σ_1R compared to the σ_2R and no studies have shown effects of σ_2R ligands, this suggests that agonist activity at the σ_1R is effective for reducing METH-induced CPP. The effect of pretreatment with σ_1R ligands on METH self-administration has not been reported, although Hiranita et al. showed that rats first trained to self-administer METH, but not heroin or ketamine, subsequently self-administered the σ_1R agonists PRE-084 and (+)-pentazocine. The effect of PRE-084 was blocked by treatment with σ_1R antagonist BD1008 but not the dopamine receptor antagonist (+)-butaclamol or opioid antagonist (−)-naltrexone (Hiranita et al., 2013b), suggesting that neither dopaminergic nor opioid mechanisms were involved. A recent report from our laboratory showed that PRE-084 treatment reduced the ability of METH to potentiate brain reward function as measured by intracranial self-stimulation (ICSS) (Sambo et al., 2017). It was previously shown that like other drugs of abuse, METH reduces the stimulation threshold for ICSS in rats (Harris et al., 2015). Our study showed that PRE-084 pretreatment decreased the ability of METH to reduce the ICSS threshold, with no effect of PRE-084 by itself (Sambo et al., 2017). Although reinforcing behavior has been less examined compared to locomotor activity, few studies similarly support a lack of effect of σ_1R ligands alone, with no reports showing aversive or rewarding effects of the σ_1R drugs. The effect of σ_1R antagonist on reinforcing behaviors seems to be under-investigated. Furthermore, the effect of σ_1R on more protracted addictive processes such as drug extinction and reinstatement, to our knowledge, has not been examined.

Toxicity

An important consequence of METH use is resultant dopaminergic neurodegeneration that is at least in part due to direct neurotoxic actions of METH on DA neurons (Bowyer et al., 1994; Broening et al., 1997; Hotchkiss and Gibb, 1980). Hyperthermia and excitotoxic NMDA receptor activation have been identified as critical mechanistic components of

METH-induced neurotoxicity (Bowyer et al., 1994; Sonsalla et al., 1989). As described above, the METH-mediated dopaminergic insult is hypothesized to increase the risk for PD in individuals with a history of METH, but not cocaine, abuse (Callaghan et al., 2012).

σ_1Rs have been investigated extensively in the context of METH-induced DA neurotoxicity due to their described neuroprotective potential and ability to modulate METH's behavioral responses (Nguyen et al., 2005). One of the first compounds examined for neuroprotection against METH-induced neurotoxicity *in vitro* and *in vivo* was the $\sigma_{1/2}$R antagonist AC927 (Matsumoto et al., 2008). Pretreatment with AC927 prior to METH (1 mg/kg) exposure not only blocked the METH-induced increases in locomotor activity but similarly blocked METH-induced (5 mg/kg) decreases in DA levels and dopaminergic immunoreactivity as well as METH-induced hyperthermia (Matsumoto et al., 2008). These results were replicated in further studies, and the protective effects of AC927 were shown to extend to the serotonergic system (Seminerio et al., 2011). Similarly, the high-affinity $\sigma_{1/2}$R antagonist CM156 was also shown to be protective against METH toxicity (Kaushal et al., 2011; Kaushal et al., 2013). Additional mechanistic insight revealed that inhibition of σ_1R with BD1047 prevented NMDA receptor induced neurotoxicity in the hippocampi of mice injected with METH (Smith et al., 2010). Furthermore, AC927 pretreatment attenuated the generation of reactive oxygen species triggered by METH in differentiated NG108-15 cells (Seminerio et al., 2011). The mechanisms by which σRs are neuroprotective specifically in the dopaminergic or serotonergic systems requires further investigation, but taken together, the ability of σ_1Rs to attenuate METH-induced hyperthermia, NMDA receptor activation in the hippocampus, and reactive oxygen species generation *in vitro* constitute the therapeutic potential of σ_1Rs against METH-induced neurotoxicity in DA neurons.

Ligands with Dual Affinity for the Sigma-1 Receptor and DAT

Several studies have investigated the role of non-selective σR binding drugs in the rewarding effects of psychostimulants. An early study using rimacozole, a benztropine compound that acts as an atypical DAT blocker with σR antagonist activity, decreased (+)SKF-10,047-induced hyperactivity but had no effect on AMPH-induced hyperactivity (Ceci et al., 1988). Similarly, a variety of benztropines as well as the combined treatment with the DA-uptake inhibitor WIN35,428 and the σR antagonist BD1008 attenuated METH self-administration with no effect on self-administration of heroin or ketamine (Hiranita et al., 2014). These studies suggest that σR antagonists capable of DAT blockade may be a viable target for METH addiction, and further support the idea that σRs may be involved in the clinical efficacy of commonly prescribed drugs with dual affinity for σRs and other targets (such as haloperidol and fluoxetine).

Potential Mechanisms

To date, there is no clear mechanistic evidence as to how the σ_1R modulates METH-mediated behavioral responses, although σ_1R-regulation of the dopaminergic system remains a potential candidate. In addition to investigating the effects of σ_1R on basal dopamine release, σ_1R ligands have also been examined for their effects on METH-stimulated dopamine release. A 2011 study by Rodvelt et al. revealed that while the σ_1R antagonists BD1047 and BD1063 did not alter METH-induced [^{3}H]DA overflow in

preloaded rat striatal slices, higher doses of the σ_1R agonist SA4503 attenuated evoked [^{3}H]DA release by METH but not nicotine (Rodvelt et al., 2011b). Recently, our laboratory similarly revealed both *in vitro* in DAT-expressing HEK cells as well *in vivo* in the mouse striatum using amperometry that the σ_1R agonist PRE-084 also attenuated METH-stimulated dopamine release, while the σ_1R antagonist BD1063 had no effect (Sambo et al., 2017). In both studies, neither the σ_1R agonists nor antagonists affected dopamine release at baseline, consistent with reports described above that ligands selective for the σ_1R, but not the σ_2R, do not influence dopamine release alone.

The molecular mechanisms by which σ_1R agonists attenuate METH-mediated dopamine neurotransmission is poorly understood. σ_1R interactions with the D_2R and DAT regulating the actions of these proteins could in turn regulate METH-stimulated dopamine release. Although the σ_1R/D_2R interaction has not been investigated in the context of METH, our laboratory showed that METH treatment alone had no effect on the interaction between σ_1R and DAT as measured by Foster Resonance Energy Transfer; however, METH exposure after treatment with the σ_1R agonist PRE-084 potentiated the σ_1R/DAT interaction. This suggests that σ_1R agonism alone does not affect its interaction with DAT but the presence of METH produces the cellular environment for the σ_1R to then association with DAT. In this study, we also revealed that σ_1R activation by the σ_1R agonist PRE-084 decreased the METH-stimulated increase in intracellular calcium, which is a crucial cellular event for METH-stimulated dopamine efflux (Sambo et al., 2017). Interactions with DAT or regulation of intracellular calcium represent potential mechanisms by which the σ_1R may reduce METH-stimulated dopamine release, which would in turn reduce METH-mediated behavioral responses. Further investigation is required to properly link these effects.

6. DISCUSSION

Overall, while the studies described in this review implicate the σ_1R in the effects of METH, results are varied regarding whether the σ_1R plays a positive or negative role in the regulation of METH-mediated responses. This variability across the field may be due to several factors. By virtue of having a wide variety of structurally and functionally different ligands targeting σRs as well as the ongoing development of novel σR ligands that have not been widely characterized across different laboratories, comparing studies using different σR drugs may not allow for accurate conclusions. Furthermore, the bioavailability and pharmacokinetics of many of the selective σ_1R ligands used have yet to be determined, further complicating the interpretation of studies regarding whether the doses or incubation times utilized are physiologically relevant to effect σ_1Rs. As such, it is difficult, if not impossible, to compare doses used *in vitro* to those used *in vivo* without knowing if the drug effectively reaches the brain at concentrations high enough to activate σ_1Rs, making *in vitro* mechanistic studies difficult to compare to functions measured in *in vivo* studies. As σ_1R agonism is canonically defined as the dissociation of σ_1R from BiP, studies showing whether σ_1R ligands can dissociate σ_1R from BiP *in vivo* would better allow researchers to understand the nature of these ligands and whether the doses used reach physiological levels that replicate *in vitro* cellular findings.

Importantly, the focus of this review was to summarize studies regarding the effects of σ_1R ligands on METH addiction, although σ_1R ligands have been investigated against other drugs of abuse. In particular, several studies have examined the effects of different σ_1R ligands in different models of cocaine addiction. It should be noted that while METH and cocaine are both psychostimulants with similar behavioral profiles, as a DAT substrate and not a DAT blocker, METH acts via different cellular mechanisms including promoting DAT-mediated reverse transport of DA, increasing the firing activity of DA neurons, stimulating DAT internalization, and increasing intracellular calcium levels, all of which are blocked by cocaine. These molecular differences should be considered as these different mechanisms may require different pharmacological treatment strategies. For example, it was recently shown that a single infusion of AMPH reversed cocaine-induced deficits in DAT function (Ferris et al., 2015). This highlights the importance in considering these classes of drugs separately as AMPHs can potentially attenuate the effects of cocaine, and vice versa. Although studies show similar effectiveness for some σR ligands across different drugs of abuse (Hiranita et al., 2013b; Mori et al., 2014), it is important to not necessarily generalize the effectiveness of σR drugs, or other drugs for that matter, across different addictive drugs.

Although the actions of σ_1R-targeting ligands remain complex, the potential therapeutic potential for σ_1R drugs is promising. One attractive feature of selective σ_1R ligands is the lack of baseline activity, suggesting minimal off-target effects. This may seem contradictory given the wide distribution of σ_1Rs as well as the large number of proteins and pathways it has been shown to modulate, but importantly the σ_1R seems to selectively elicit responses under stimulated or pathological conditions. This, in theory, would suggest that in cells at physiological homeostasis, ligand activation or inhibition of σ_1Rs would not provoke a response. Along these lines, many selective σ_1R ligands also do not show rewarding effects on their own, which is an important feature when considering pharmacotherapies for the treatment of drug abuse. Several clinically used drugs have appreciable affinity for the σ_1R, including the antipsychotic haloperidol and the antidepressants fluoxetine and sertraline, supporting the efficacy of σ_1R-targeting drugs for the treatment of psychiatric disorders. Selective σ_1R ligands have been investigated in clinical trials for the treatment of neuropathic pain (Abadias et al., 2013; Collina et al., 2013), neurodegenerative disease (Collina et al., 2013), anxiety (Moller et al., 2001), depression (Moller et al., 2003; Volz et al., 2000), and schizophrenia (Frieboes et al., 1999; Frieboes et al., 1997; Gewirtz et al., 1994; Huber et al., 1999; Niitsu et al., 2012). Although these studies overall indicate the safety and tolerability of the drugs tested, the efficacy of these drugs remains inconclusive. To our knowledge, clinical trials investigating the effect of σ_1R ligands for psychostimulant abuse are not reported; however, the efficacy of different σ_1R drugs in reducing the effects of METH in different preclinical models of METH addiction and reported safety of σ_1R ligands in humans support further investigation of the σ_1R as a target for METH abuse.

ABBREVIATIONS

AC927	1-(2-phenylethyl)piperidine
AMPH	amphetamine

ATS	amphetamine-type stimulants
AZ66	3-(4-(4-cyclohexylpiperazin-1-yl)pentyl)-6-flourobenzo(Abadias et al., 2013)thiazol-2(3*H*)-one
BD1008	N-(Brammer et al., 2006)-N-methyl-1-pyrrolidineethanamine
BD1047	N-(Brammer et al., 2006)-N-methyl-2-(dimethylamino)ethylamine
BD1063	1-(Jones et al., 1998)-4-methylpiperazine
BiP	binding immunoglobulin protein
BMY 14802	alpha-(4-fluorophenyl)-4-(5-fluoro-2-pyrimidinyl)-1-piperazine-butanol
CM156	3-(4-(4-cyclohexylpiperazin-1-yl)butyl)benzo[*d*]thiazole-2(3*H*)-thione
CPP	conditioned place preference
DA	dopamine
DAT	dopamine transporter
DMT	N,N-dimethyltryptamine
DTG	1,3-di-O-tolylguanidine
MDMA	Methylenedioxy-methamphetamine
METH	methamphetamine
MS-377	(R)-(+)-1-(4-chlorophenyl)-3-[4-(2-methoxyethyl)piperazin-1-yl]me thyl 2- pyrrolidinone L-tartrate
NE-100	4-methoxy-3-(2-phenylethoxy)-N,N-dipropylbenzeneethanamine
NMDA	N-methyl-D-aspartate
PCP	phencyclidine
PD	Parkinson’s disease
PKC	protein kinase C
PRE-084	2-(4-Morpholinethyl) 1-phenylcyclohexanecarboxylate hydrochloride

SA4503	1-(3,4-dimethoxyphenethyl)-4-(3-phenylpropyl)piperazine dihydrochloride
SKF-10,047	N-allylnormetazocine ((−)-ANMC)
SN	substantia nigra
VMAT2	vesicular monoamine transporter-2
VTA	ventral tegmental area
σ_1R	sigma-1 receptor
σ_2R	sigma-2 receptor

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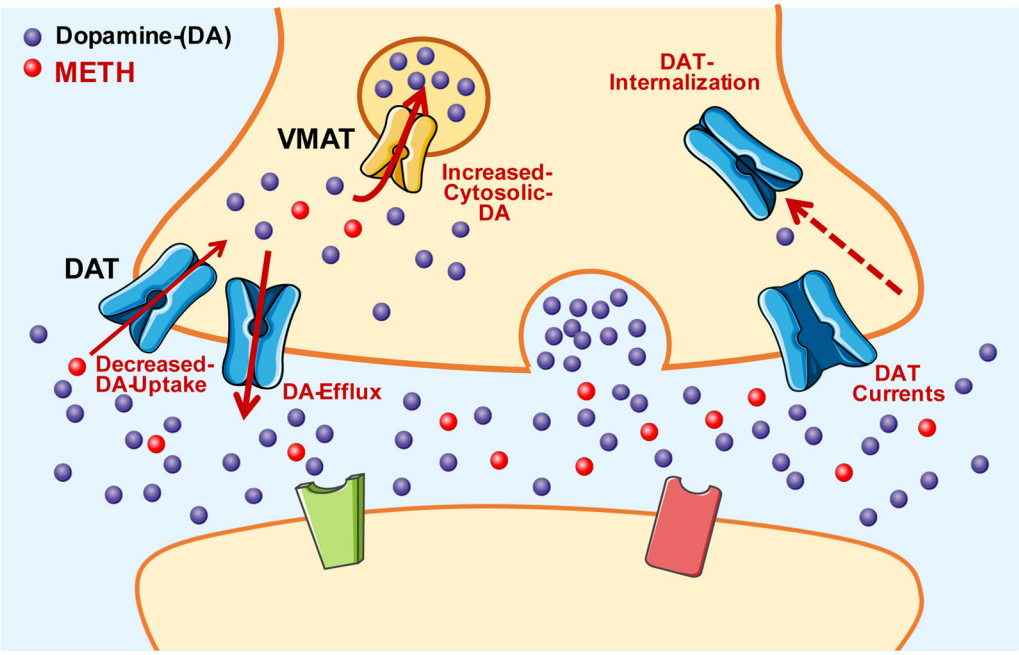

Figure 1.
METH-stimulated, DAT-mediated increase in extracellular dopamine. Molecule and protein images are courtesy of Servier Medical Art, licensed under CC BY 3.0.

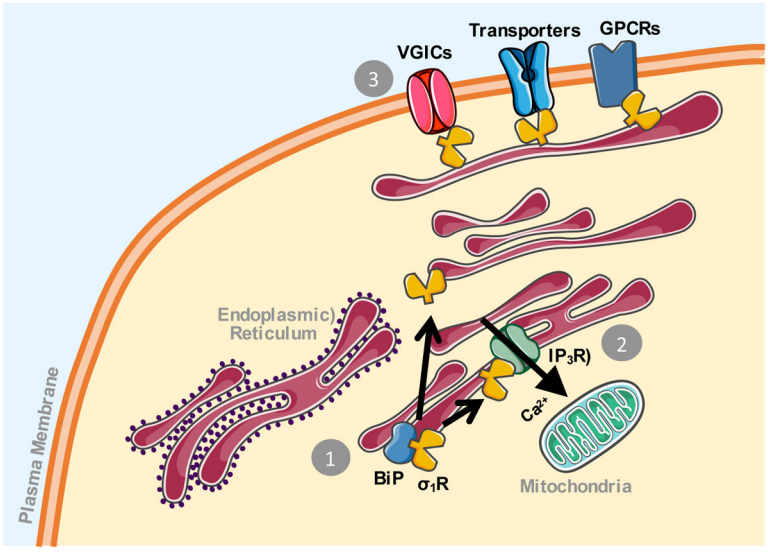

Figure 2.

Schematic of sigma-1 receptor cellular activity. **(1)** The sigma-1 receptor (σ_1R) is constitutively bound to another endoplasmic reticulum protein Binding Immunoglobulin Protein (BiP). Upon activation, the σ_1R dissociates from BiP where it can then translocate to other cellular compartments. **(2)** The σ_1R has been shown to stabilize IP_3 type 3 receptors at the mitochondrial associated membrane and promote calcium (Ca^{2+}) influx into the mitochondria. This promotes cellular metabolism and contributes to the pro-survival effects of the σ_1R. **(3)** The σ_1R has also been shown to associate with and regulate the activity of different membrane proteins, including voltage-gated ion channels (VGICs), transporter proteins, and G-protein coupled receptors (GPCRs). The ER, mitochondria, and protein images are courtesy of Servier Medical Art, licensed under CC BY 3.0.

Table 1

Ligand Affinities for σ_1R, σ_2R, and DAT (K_i, nM)

Stimulants and Psychiatric Drugs					
Ligand	**Activity**	**σ_1R**	**σ_2R**	**DAT**	**Reference**
Cocaine	Agonist	n.d.	n.d.	164	Izenwasser et al., 1999
		5,190	19,300	77	Garcés-Ramírez et al., 2012
		1,347	48,170	n.d.	Lever et al., 2016
Fluoxetine	Agonist	240	16,100	n.d.	Narita et al., 1996
Haloperidol	Antagonist	7.0	n.d.	n.d.	Su, 1982
		1.9	79.8	n.d.	Bowen et al., 1993
		n.d.	n.d.	5,232	Izenwasser et al., 1993
		3.3	270.0	n.d.	Takahashi et al., 1999
		2.2	16.0	9,578	Moison et al., 2003
		0.9	7.9	n.d.	Lever et al., 2006
		1.2	18.1	n.d.	Lever et al., 2014
		1.4	72.8	n.d.	Lever et al., 2016
Methamphetamine	???	†2,160	†46,670	n.d.	Nguyen et al., 2005
		4,390	15,900	n.d.	Hiranita et al., 2013
MDMA	???	3,057	8,889	10,320	Brammer et al., 2006
Sertraline	Agonist	57	5,297	n.d.	Narita et al., 1996

Selective σ Ligands					
Ligand	**Activity**	**σ_1R**	**σ_2R**	**DAT**	**Reference**
(+)-3-PPP	Agonist	49.3	120.0	n.d.	Bowen et al., 1993
		n.d.	n.d.	1,784	Izenwasser et al., 1993
AC927	Antagonist	30.0	138.0	2,939	Matsumoto et al., 2008
AZ66	Antagonist	2.4	0.5	872	Seminerio et al., 2012

Selective σ Ligands

Ligand	Activity	σ_1R	σ_2R	DAT	Reference
		4.7	1.4	1,950	Katz et al., 2016
BD1008	Antagonist	2.0	8.0	n.d.	McCrackena et al., 1999
		2.1	16.6	2,510	Garcés-Ramírez et al., 2012
BD1047	Antagonist	0.9	47.0	n.d.	Matsumoto et al., 1995
		3.0	48.0	3,220	Garcés-Ramírez et al., 2012
BD1063	Antagonist	9.2	449.0	n/a	Matsumoto et al., 1995
		6.0	440.0	16,820	Brammer et al., 2006
		9.0	625.0	8,020	Garcés-Ramírez et al., 2012
		8.8	626.0	8,020	Katz et al., 2016
		9.7	762.0	n.d.	Lever et al., 2016
BMY-14802	Antagonist	265.0	391.0	n.d.	Weigl et al., 2002
CM156	Antagonist	1.3	0.6	1,175	Xu et al., 2010
DTG	Agonist	74.3	61.2	n.d.	Bowen et al., 1993
		69.0	21.0	>10,000	Moison et al., 2003
		35.5	39.9	n.d.	Lever et al., 2006
		57.0	22.0	93,500	Garcés-Ramírez et al., 2012
		111.8	39.1	n.d.	Lever et al., 2016
MR200	Agonist	1.5	21.9	>10,000	Moison et al., 2003
MS-377	Antagonist	73.0	6,900.0	n.d.	Takahashi et al., 1999
NE100	Antagonist	*1.5	*633.0	n.d.	Chaki et al., 1994
		2.5	121.0	3,590	Hiranita et al., 2011
(+)-Pentazocine	Agonist	6.7	1,361	n.d.	Bowen et al., 1993
		1.6	728.4	n.d.	Lever et al, 2006
		4.6	224.0	n.d.	Hiranita et al., 2013
		5.1	2,060.0	n.d.	Lever et al., 2016

Selective σ Ligands

Ligand	Activity	σ_1R	σ_2R	DAT	Reference
PRE-084	Agonist	*44.0	n.d.	n.d.	Su et al., 1991
		n.d.	n.d.	5,344	Izenwasser et al., 1993
		46.5	n.d.	n.d.	Cao et al., 2003
		48.5	12,700.0	n.d.	Hiranita et al., 2013
		53.0	32,100.0	19,600	Garcés-Ramírez et al., 2012
SA4503	Agonist	*17.4	*1,784.0	n/a	Matsuno et al., 1996
		4.6	63.1	n.d.	Lever et al., 2006
(+)-SKF-10,047	Agonist	28.7	33,654.0	n.d.	Bowen et al., 1993

Other Drugs

Ligand	Activity	σ_1R	σ_2R	DAT	Reference
DHEA-sulfate	Agonist	15,129	n.d.	n.d.	Maurice et al., 1996
DMT	???	†14,750	†21,710	n.d.	Fontanilla et al., 2009
PCP	???	*2,541	n.d.	n.d.	Su, 1982
Progesterone	Antagonist	175	n.d.	n.d.	Maurice et al., 1996
		2.7	n.d.	n.d.	Su et al., 1988
Rimacozole	Antagonist	908.0	302.0	224	Husbands et al., 1999
		96.6	883.0	238	Hiranita et al., 2011

n.d.: not determined,

†K_D,

*IC50