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# 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 a 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 ($\sigma_1$R). The $\sigma_1$R 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 $\sigma_1$R regulates a variety of cellular functions and possesses neuroprotective activity in the brain. Interestingly, a variety of $\sigma_1$R ligands modulate dopamine neurotransmission and reduce the behavioral effects of METH in animal models of addictive behavior, suggesting that the $\sigma_1$R may be a viable therapeutic target for the treatment of METH addiction. In this review, we provide background on METH and the $\sigma_1$R as well as a literature review regarding the role of $\sigma_1$Rs in modulating both dopamine neurotransmission and the effects of METH. We aim to highlight the complexities of $\sigma_1$R pharmacology and function as well as the therapeutic potential of the $\sigma_1$R as a target for the treatment of METH addiction.



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## 1. Introduction

Methamphetamine (METH) is one of the most commonly used illicit drugs in the world (Krasnova & Cadet, 2009), with reports that up to 35 million people use amphetamine-type stimulants (ATSs) worldwide (Salamanca, Sorrentino, Nosanchuk, & Martinez, 2014). Although there have been clinical trials for drugs targeting the dopaminergic, serotonergic, and opioid systems (Karila et al., 2010), there are

*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]methyl2-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; $\sigma_1$R, sigma-1 receptor; $\sigma_2$R, sigma-2 receptor.

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currently no Food and Drug Administration (FDA) approved pharmacotherapies for the treatment of METH addiction (Napier, Herrold, & de Wit, 2013). While it is well established that METH elicits its addictive effects primarily through interactions with the dopamine transporter (DAT) (Sulzer, Maidment, & Rayport, 1993), growing evidence indicates that sigma receptors (σRs) may be involved in METH addiction. Two isoforms of σRs are known to exist, $\sigma_1$R and $\sigma_2$R; however, the $\sigma_1$R has been more thoroughly characterized in the literature (Bowen, 2000; Quirion et al., 1992). In addition to responding to cellular stress, the $\sigma_1$R is a ligand-operated chaperone protein that can be activated or inhibited by different ligands in an agonist-antagonist manner (Hayashi & Su, 2003b; Tsai, Hayashi, Mori, & Su, 2009). Several $\sigma_1$R-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 $\sigma_1$R, supporting the therapeutic potential of drugs targeting $\sigma_1$Rs. 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 $\sigma_1$R ligands every year and the increased understanding of the protein's function, the $\sigma_1$R remains a highly attractive therapeutic target for METH addiction.

## 2. Methamphetamine

### 2.1. 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 & 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, Greenberg, Miller, Okaneku, & Haggerty, 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 & 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 and 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.

### 2.2. 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 & Ray, 2014; Rawson & 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, Reus, Wolkowitz, Mendelson, & Jones, 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 & Ray, 2014). Conversely, METH can also induce acute negative psychological effects including anxiety, insomnia, aggressive behavior, paranoia, and psychosis (Rawson & Condon, 2007). At high doses, METH can elevate the body temperate to potentially lethal levels, resulting in convulsions, coma, stroke, or even death (Rawson & 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 & Condon, 2007). Long-term chronic METH use often leads to the development of symptoms including violent behavior, anxiety, cognitive impairment, and insomnia (Rawson & 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, Stein, & Howells, 2014). Additional adverse physiological consequences of prolonged METH use include cardiovascular problems, pulmonary disease, and infections from repeated intravenous injections (such as HIV) (Rawson & Condon, 2007). Patterns of METH abuse may also lead to other negative repercussions including disrupted personal relationships, unemployment, and incarceration (Hsieh et al., 2014).

### 2.3. 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 & Rutledge, 1973; Halpin, Collins, & Yamamoto, 2014). Both the rewarding and addictive properties of ATSs are primarily attributed to their ability to increase extracellular DA levels (Sonders, Zhu, Zahniser, Kavanaugh, & Amara, 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 & Smith, 1975; Gunne, Anggard, & Jonsson, 1972; Jonsson, Anggard, & Gunne, 1971; Yokel & 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 & 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., 1999; Volkow, Fowler, Wang, Swanson, & Telang, 2007). 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.

### 2.4. Methamphetamine interactions with DAT

Dopamine (DA) is important for regulating processes including reward, motivation, movement, working memory, and cognition (Chinta & 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

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