

Review Article

Potential Molecular Mechanisms on the Role of the Sigma-1 Receptor in the Action of Cocaine and Methamphetamine

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Abstract The sigma-1 receptor (Sig-1R) is an endoplasmic reticulum membrane protein that involves a wide range of physiological functions. The Sig-1R has been shown to bind psychostimulants including cocaine and methamphetamine (METH) and thus has been implicated in the actions of those psychostimulants. For example, it has been demonstrated that the Sig-1R antagonists mitigate certain behavioral and cellular effects of psychostimulants including hyperactivity and neurotoxicity. Thus, the Sig-1R has become a potential therapeutic target of medication development against drug abuse that differs from traditional monoamine-related strategies. In this review, we will focus on the molecular mechanisms of the Sig-1R and discuss in such a manner with a hope to further understand or unveil unexplored relations between the Sig-1R and the actions of cocaine and METH, particularly in the context of cellular biological relevance.

Keywords sigma-1 receptor; drug abuse; cocaine; methamphetamine

1. Introduction

1.1. The history of sigma receptors

Sigma receptors were first identified from the behavioral and pharmacological studies, and were suggested as a subtype of opioid receptors known as the “sigma opioid receptor” [1]. Martin et al. proposed that three distinguishable receptors (μ , κ , and sigma receptors) contribute to distinct symptomatology induced by opioids. Since the prototypic sigma agonist, (+)SKF-10,047, produced hallucinogenic effects, sigma receptors were believed to specifically mediate the psychotomimetic effects of opioids. Later studies, however, indicated that the sigma receptor has certain features that distinguish it from other opioid receptors: (1) the SKF-10,047 binding protein has different stereospecificity from that of other opioid receptors (i.e., affinity at sigma receptors: dextrorotatory isomer > levorotatory; at opioid receptors: levorotatory > dextrorotatory); (2) the (+)SKF-10,047 binding protein has very low affinity for opioid antagonists such as naloxone and naltrexone [2,3]; (3) naltrexone does not antagonize SKF-10,047-induced behavioral effects [4].

Further studies from ligand binding assays revealed that there are two subtypes of sigma receptors, sigma-1 and sigma-2 [5,6,7,8,9]. Sigma-2 receptor (Sig-2R) has a reversed stereoselectivity (levorotatory > dextrorotatory) for sigma ligands such as SKF-10,047 and pentazocine from that of sigma-1 receptor (Sig-1R). The existence of Sig-1R and Sig-2R was strongly supported by the evidence from photoaffinity labeling studies which showed that the Sig-1R and the Sig-2R consist of 25 kDa and 18–21.5 kDa polypeptides, respectively [8,9,10]. The Sig-1R has been cloned and the sequence shows no significant homology with that of any of other mammalian proteins including opioid receptors [11]. At present, it is recognized that the Sig-1R is a nonopioid, non-G protein-coupled intracellular receptor comprised of a 24 kD single protein [12,13,14]. On the other hand, the Sig-2R has not yet been cloned. Although Xu et al. identified the Sig-2R as the progesterone receptor membrane component 1: PGRMC1 [15], there exists certain controversy regarding, for instance, its molecular size which seems to be different from that of the Sig-2R. Further, the Sig-2R could still be specifically photoaffinity labeled in the PGRMC1 knockout cells [16,17,18].

1.2. Physiological functions of sigma receptors

Sigma receptors are expressed ubiquitously throughout many organs [9,11,13,36,37,38,39,40,41]. The functions of Sig-1R have been intensely investigated especially in the central nervous system (CNS). The Sig-1R has been implicated in neuropsychiatric diseases [42,43] such as depression [44], anxiety, and schizophrenia [45], partly because the Sig-1R binds to many psychotomimetic and psychiatric drugs. In addition, it has been suggested that the Sig-1R promotes a positive effect on memory and learning processes [46,47]. Also, the Sig-1R seems to be neuroprotective in nature [48] and thus plays a role in neurodegenerative disorders such as Alzheimer’s disease [49], Parkinson’s

Table 1: Affinity of cocaine and METH at Sig-1R and Sig-2R.

	Sample/reference	Affinity for Sig-1R	Affinity for Sig-2R
Cocaine	Rat cerebellum [19]	$6.7 \pm 0.3 \mu\text{M}^{*1}$	
	Mouse brain [20]	$2 \pm 0.2 \mu\text{M}^{*2}$	$31 \pm 4 \mu\text{M}^{*3}$
	Guinea pig brain minus cerebellum [21]	5,190 (3,800–7,060) nM ^{*2}	19,300 (16,000–23,300) nM ^{*3}
METH	Rat brain [22]	$2.16 \pm 0.25 \mu\text{M}^{*2}$	$46.67 \pm 10.34 \mu\text{M}^{*3}$
	Guinea pig brain minus cerebellum [23]	4,390 (3,740–5,160) nM ^{*2}	15,900 (11,700–21,500) nM ^{*3}

*¹in competition with haloperidol.

*²in competition with (+)-pentazocine.

*³in competition with DTG in the presence of (+)-pentazocine.

Table 2: Peak concentrations of cocaine and METH in the blood, plasma or brain.

	Drug administrating condition/reference	Blood or plasma	Brain
Acute cocaine	Mouse, 10 mg/kg, IP [24]	0.75 $\mu\text{g}/\text{mL}$	2.6 $\mu\text{g}/\text{g}$
	Mouse, 25 mg/kg, IP [24]	1.5 $\mu\text{g}/\text{mL}$	6.7 $\mu\text{g}/\text{g}$
	Rat, 8 mg/kg, IV [25,26]	$0.61 \pm 0.06 \mu\text{g}/\text{mL}$	$7.27 \pm 0.18 \mu\text{g}/\text{g}$
	Rat, 20 mg/kg, SC [25,26]	$0.49 \pm 0.06 \mu\text{g}/\text{mL}$	$3.44 \pm 0.36 \mu\text{g}/\text{g}$
	Rat, 30 mg/kg, IP [27]	2.7 μM	$1.41 \pm 0.09 \mu\text{M}^*$
Chronic cocaine	Rat, 20 mg/kg, SC for 3 weeks, twice a day [25]	$0.50 \pm 0.10 \mu\text{g}/\text{mL}$	$3.05 \pm 0.14 \mu\text{g}/\text{g}$
	Rat, 10–20 mg/kg, SC for 10 or 30 days, once a day,	10 days, 4.1 μM	10 days, 2.62 μM^*
	30 mg/kg, IP on the test day [27]	30 days, 5.5 μM	30 days, 1.8 μM^*
	Human, 20.5 mg, IV [28]	$180 \pm 56 \text{ ng}/\text{mL}$	
	Human, 94.6 mg, NI [28]	$220 \pm 50 \text{ ng}/\text{mL}$	
	Human, 50 mg, SI [28]	$203 \pm 88 \text{ ng}/\text{mL}$	
Acute METH	Mouse, 2.5 mg/kg, IP [29]		$2.63 \pm 0.27 \mu\text{g}/\text{g}$
	Mouse, 5.0 mg/kg, IP [29]		$4.96 \pm 0.35 \mu\text{g}/\text{g}$
	Mouse, 10 mg/kg, IP [29]		$8.90 \pm 0.40 \mu\text{g}/\text{g}$
	Rat, 1 mg/kg, SC [30]	7.5 ng/mL	70 ng/g
	Rat, 5 mg/kg, SC [30]	40 ng/mL	300 ng/g
	Rat, 0.5 mg/kg, IV [31]	$0.54 \pm 0.07 \mu\text{M}$	
	Rat, 2.5 mg/kg, IV [32]	$1.0 \pm 0.1 \mu\text{g}/\text{mL}$	
Chronic METH	Rhesus monkey, 0.32 mg/kg, IM [33]	$51.0 \pm 8.5 \text{ ng}/\text{mL}$	
	Human, 30 mg, IV [34]	175 ng/mL	
	Human, 15.5 mg, IV [35]	100 ng/mL	

*Extracellular concentrations in the nucleus accumbens.

disease, amyotrophic lateral sclerosis (ALS), and strokes [50,51]. Interestingly, because clinically available drugs for those psychiatric and neurodegenerative disorders are quite limited, the Sig-1R ligands are being explored to serve as new therapeutic agents for those diseases. In addition, the involvement of the Sig-1R in cancer, immune system, neuropathic pain [52], cardiac functions [53], and retinal disease has been reported. Regarding the Sig-2R, studies on its specific functions have been difficult partly because of the low selectivity of ligands and because of the lack of information on its sequence. Nevertheless, as highly selective ligands for Sig-2R are being developed, there is a strong notion that the Sig-2R relates to cancer. For example, the Sig-2R expression is dramatically elevated in various tumor cells and Sig-2R agonists cause apoptosis and tumor cell death [54,55,56]. The Sig-2R has thus been recently receiving more attention as a potential biomarker of proliferation [54,57,58]. It also has been suggested that

Sig-2R ligands possess antidepressant-like effects [59] and may also attenuate the learning impairment [47].

1.3. Drug abuse and sigma receptors

Sigma receptors have been implicated in the addictive process and toxicity induced by psychostimulants. Cocaine and methamphetamine (METH) have been mostly studied in this regard because cocaine and METH bind to the Sig-1R at physiologically relevant concentrations [24,25,26,27,28,29,30,31,32,33,34,35] (cocaine at 2–7 μM and METH at 2–4 μM), however, they bind to the Sig-2R with lower affinities (cocaine at 19–31 μM and METH at 16–47 μM) [19,20,21,22,23] (Tables 1 and 2). Also, cocaine and METH are among the most abused substances in the world, and currently effective medications are lacking against the addiction and toxicity of those two drugs. Therefore, sigma receptors and associated ligands have been explored as therapeutic targets against cocaine and METH.

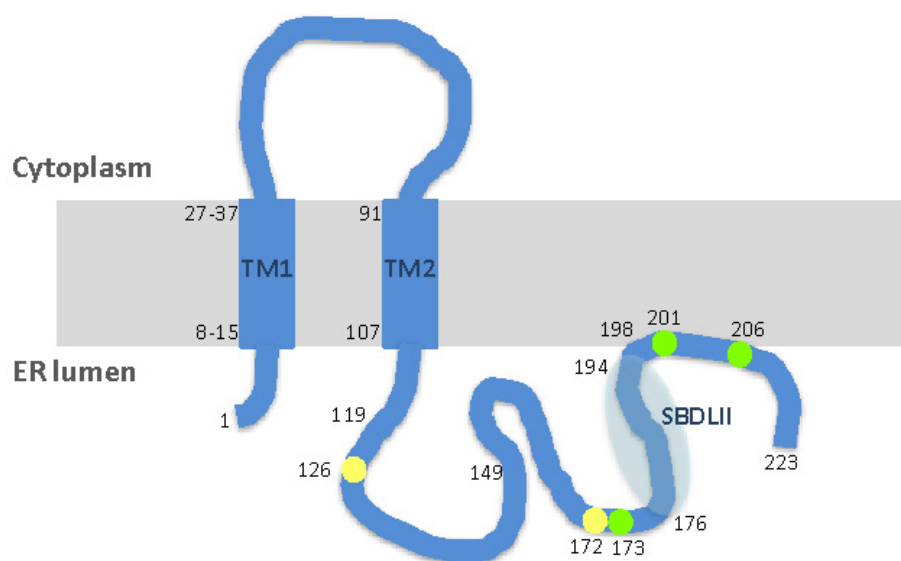


Figure 1: A schematic presentation of predicted topology and ligand binding regions of Sig-1R. The numbers represent amino acid (a.a.) residues. The colored circles show the a.a. residues critical for Sig-1R binding to haloperidol (yellow) and cholesterol (green), respectively. The TM2 and SBDLII are suggested to compose the ligand binding region of Sig-1R. A splice variant of Sig-1R, which lacks a.a. 119-149 region, is devoid of ligand binding. Abbreviations: ER, endoplasmic reticulum; TM, transmembrane domain; SBDLII, sterol-binding domain like-II.

Cocaine is most likely an agonist for the Sig-1R since the cocaine effects are blocked by Sig-1R antagonists. In contrast, Sig-1R agonists often mimic or potentiate the effect of cocaine. METH possibly acts like an agonist at the Sig-1R for the same reasons as cocaine does. However, METH seemingly acts like an inverse agonist in the Sig-1R-Bip association test (see Section 2.2). The exact biochemical relation between METH and the Sig-1R remains to be totally clarified.

Interestingly, subtype nonselective sigma receptor antagonists are often more effective in inhibiting the METH effects, suggesting that there may be some unknown synergistic relation between Sig-1R and Sig-2R. In fact, a number of pharmacological studies have demonstrated that antagonists of sigma receptors, mostly Sig-1R-preferring only or nonselective for Sig-1R and Sig-2R, attenuate the effects of cocaine and METH in rodents. For example, pretreatment with selective Sig-1R antagonists attenuates hyperactivity, behavioral sensitization, and conditioned place preference (CPP) induced by cocaine; and the locomotor hyperactivity stimulated by METH. Also, Sig-1R selective antagonists mitigate cellular and behavioral toxicities induced by cocaine including convulsion and death while nonselective antagonists counteract METH-induced neuronal degeneration [60,61,62]. In general, specific involvement of the Sig-2R in this regard has just begun to be understood. For example, a selective Sig-2R antagonist counteracts cocaine-mediated locomotion activity [63]. However, the precise molecular mechanisms

between the actions of those two abused drugs and the roles of sigma receptors are not fully understood.

Since the sequence of the Sig-1R is known and some progresses for understanding the Sig-1R's molecular functions have been made, this review will focus on the Sig-1R and the associated molecular mechanisms. At first we will provide the biological information on Sig-1R, and then discuss the molecular basis of the Sig-1R as it relates to the actions of cocaine and METH including in particular the addictive process and toxicity.

2. Biology of the Sig-1R

2.1. Structure and ligand binding

The Sig-1R is a 223 amino acid (a.a.) transmembrane protein that possesses two transmembrane domains (TMs): one at the N-terminus (TM1: predicted as an about 20 a.a. spanning between residues 8 ~ 15 and 27 ~ 37) and the other at the center (TM2: a.a. residues 91–107, also referred to as sterol-binding domain like-I (SBDLI) [64]). A membrane-attached region at the C-terminus (a.a. residues 198–206) was suggested from solution NMR studies [13,65,66,67] (Figure 1). The Sig-1R protein is highly conserved in various mammalian species with over 90% of similarity in the a.a. sequence [36]. The Sig-1R shared no homology with any of other mammalian proteins, but shares a 30% homology with a yeast C7-C8 sterol isomerase [11]. The homology resides mainly between the sterol-binding pocket of the C7-C8 sterol isomerase and TM2, and a hydrophobic region (a.a. residues 176–194, referred to as SBDLII in [64]) at the

C-terminus of Sig-1R [11]. The homology, though limited, suggests that the Sig-1R has affinity for sterols [68]. Palmer et al. examined the Sig-1R-cholesterol interaction and found that tyrosines 173, 201, and 206 play a critical role for the Sig-1R to bind cholesterol [69]. Several sterols and lipids have been proposed as endogenous ligands of Sig-1R. A number of studies showed that progesterone binds to Sig-1R and competes with sigma ligands at the physiologically relevant concentrations [68], suggesting certain functionalities in vivo [70]. By using the unique property of sigma ligands in which agonists enhance the action of NMDA receptor while antagonists, being devoid of effect by themselves, block the effect caused by agonists, Bergeron et al. proposed progesterone as an antagonist and dehydroepiandrosterone (DHEA) as an agonist at the Sig-1R [71]. In addition, sphingosine [72], monoglycosylated ceramide [73], 25-dehydroxycholesterol [74], and myristic acid [75] have been shown to have high affinities for the Sig-1R. Further studies are needed to clarify the physiological and functional relevance of the Sig-1R-lipid interaction except for the Sig-1R-myristic acid interaction which has been shown to play a critical role in axon elongation [75].

Photoaffinity labeling studies combined with biochemical approaches have revealed that TM2 and SBDLII are juxtaposed to form, at least in part, the Sig-1R ligand binding region because point mutation in TM2 causes a decrease of the ligand binding ability [76]. The possibility exists that TM1 is also in the proximity to SBDLII and contributes thus to the binding of ligands [77]. A splice variant of Sig-1R, which lacks a.a. residues 119–149, was found to be nonfunctional in the ligand binding assay in a Jurkat human T-lymphocyte cell line [78], suggesting that the C-terminal region following TM2 is important for the ligand binding to Sig-1R. Seth et al. reported two essential a.a. residues, Asp126 and Glu172, for the haloperidol binding to Sig-1R [41]. Since TM2 and SBDLII are hydrophobic in nature, it is reasonable to assume that the hydrophobicity somehow contributes to the binding between lipids, or otherwise hydrophobic part(s) of sigma ligands, and the Sig-1R. Additionally, the negative charge of anionic a.a. including Asp126 and Glu172 between TM2 and SBDLII is possibly utilized by the Sig-1R to interact with sigma ligands that are positively charged. The positively charged hallucinogen *N,N*-dimethyltryptamine (DMT) apparently functions at least in part through Sig-1R even though the affinity of DMT at Sig-1R is in the micromolar range [79]. In contrast to that seen in wild type mice, Sig-1R knockout mice failed to respond behaviorally to DMT [66].

2.2. Molecular chaperone activity and the ligand effects

It has been demonstrated that the C-terminus of Sig-1R has a chaperone activity that assists proteins to fold properly to

ensure their functionality. The Sig-1R is a unique chaperone in that it consists of two transmembrane domains and that it is a ligand-regulated chaperone. The second transmembrane domain, in addition to being important in ligand binding, apparently plays an important role in Sig-1R interaction with other transmembrane proteins [74,80]. Because the Sig-1R chaperone, being a transmembrane itself, tends to interact more with other transmembrane proteins including many ion channels and receptors, it is tempting to speculate that this cross-interaction between transmembrane regions of a chaperone and its client protein may have an as-yet-unknown special significance in the action of the Sig-1R as a chaperone. Further studies are required to clarify this seemingly important speculation.

At the endoplasmic reticulum (ER), the C-terminus of Sig-1R faces the ER lumen and interacts with another chaperone protein Bip/GRP78 [13]. The Sig-1R interaction with Bip/GRP78 prevents the Sig-1R's chaperone activity. Sigma agonists cause the dissociation of Bip/GRP78 from the Sig-1R, resulting in the unleashing of the chaperone activity of the Sig-1R. Sigma antagonists inhibit the agonist's effect on the Sig-1R-Bip/GRP78 interaction (Figure 2). Although the Sig-1R is implicated in a wide variety of physiological functions, how and why those functions specifically relate to the chaperone activity of the Sig-1R remains to be fully understood. The detailed molecular functions of Sig-1R as a chaperone will be discussed later.

2.3. Intracellular localization of Sig-1R

The Sig-1R predominantly localizes in the ER where all of the transmembrane proteins as well as lipids for most of cellular organelles are produced. The Sig-1R is concentrated especially in the mitochondria-associated ER membrane (MAM). The MAM is a dynamic lipid-raft like domain in the ER which is enriched in cholesterol and ceramides and is thus different from a normal ER membrane [73,81]. The interaction with lipids such as cholesterol and ceramides may be important for the Sig-1R to localize at the MAM since cholesterol or ceramide depletion from lipid raft causes a decreased partitioning of the Sig-1R at the MAM.

The MAM enables metabolites and signaling molecules to exchange between the ER and mitochondria. The exchange plays a crucial role in various cellular functions of physiological and pathological significance [82]. It has been established that the MAM is the central location to regulate lipid transfer and rapid transmission of Ca^{2+} signaling between the ER and mitochondria, the latter serving to enhance the mitochondrial bioenergetics [83]. Additionally, the MAM is beginning to be understood as having a role in energy metabolism, cellular survival, redox status, ER stress, autophagy, and inflammasome signaling [84]. Recent studies elucidating new molecular functions of Sig-1R are closely paying attention to the cellular events at the MAM.

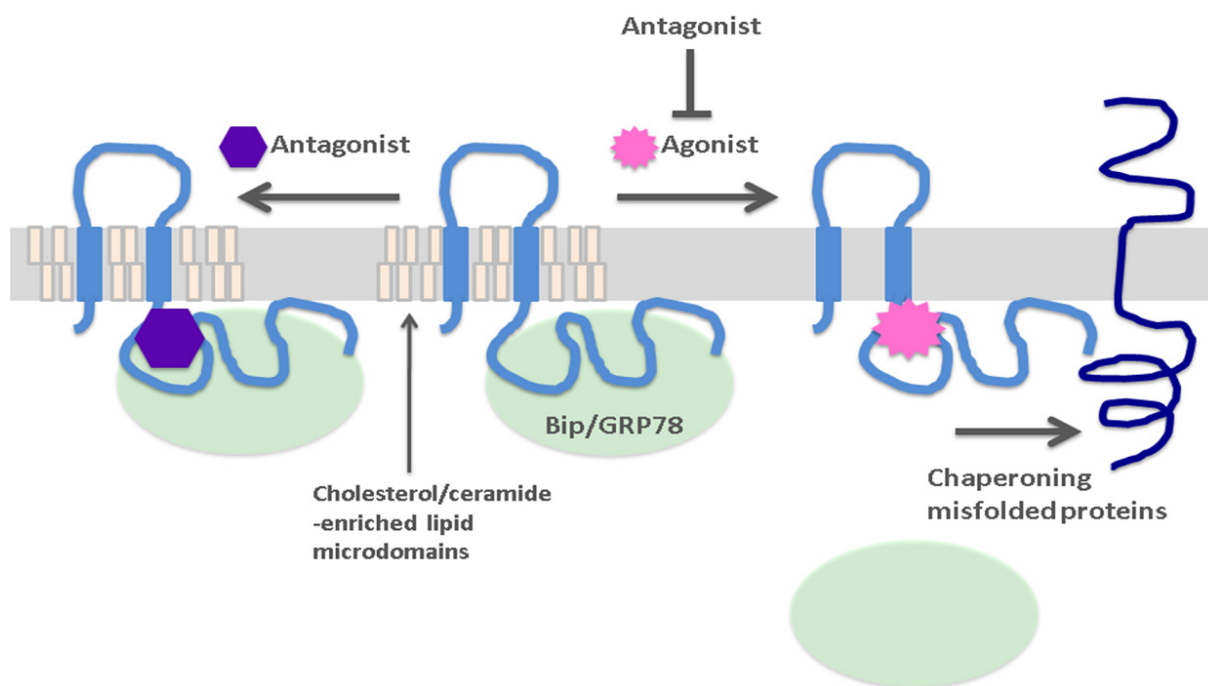


Figure 2: *Sig-1R chaperone activity and the ligand effects.* Sig-1R resides at the MAM which is enriched in cholesterol and ceramide. Sig-1R physically associates with Bip/GRP78 which inhibits the Sig-1R's chaperone activity. Upon stimulation by agonists, Sig-1R dissociates from Bip/GRP78 and chaperones misfolded proteins. Antagonists by themselves do not disrupt the interaction between Sig-1R and Bip/GRP78 but, if pretreated before agonists, can block the Sig-1R-BiP dissociation caused by the agonist.

In particular, the Sig-1R might contribute to the formation of the MAM [85,86].

Although the detailed mechanisms remain to be fully elucidated, it is believed that the Sig-1R subcellular localization is dynamically changed when cells or neurons are stimulated with Sig-1R agonists or are under cellular stress. The mobilized Sig-1R can translocate from the ER to its contiguous structures including the nuclear envelope, sub-plasmalemmal ER, and even into the plasma membrane. In fact, the existence of the Sig-1R at the plasma membrane has been shown by using biochemical methods in the Sig-1R transfected cells [87,88]. On the other hand, immunoelectron microscopy studies indicate that the endogenous Sig-1R is present at the subplasmalemmal ER but not at the plasma membrane as seen in motor neurons and retinal neurons [89,90]. A number of studies suggest that the Sig-1R modulate functions of plasma membrane proteins such as ion channels and G protein-coupled receptor through the direct protein-protein interaction. Given what we just discussed above, it can be envisioned that there are two possible ways that the Sig-1R can regulate target proteins at the plasma membrane: (1) Sig-1R and target proteins are both present at the plasma membrane and can interact with each other; (2) the Sig-1R at the subplasmalemmal ER can interact with target proteins at the plasma membrane via

close proximity. There is also the possibility that the Sig-1R may interact with target proteins at the ER, leading to affecting the target protein's function at the plasma membrane. Further studies may clarify the dynamics of the Sig-1R as it relates to its interaction with other target proteins and their resultant subcellular localization.

3. Sig-1R-related molecular mechanisms and the actions of cocaine and METH

3.1. Cocaine and METH

It is widely believed that cocaine and amphetamine-like psychostimulants including METH produce the rewarding effect by increasing dopamine (DA) transmission in the limbic system, especially in the nucleus accumbens (NAc) and prefrontal cortex (PFC), both relating to the ventral tegmental area (VTA) of the brain. The resultant activation of the dopamine receptors is also involved in the rewarding effect. However, the dynamic downstream consequences are not fully understood. In addition, establishing an addictive process apparently involves other dopamine-independent pathway(s).

It has been well known that METH causes damage and degeneration of dopaminergic neurons in various brain regions including striatum through various processes such as the activation of DA receptors, oxidative and

ER stress, and inflammation. The dopaminergic neuronal damage induced by METH is implicated in psychosis, memory impairment, and motor defects. Indeed, it has been suggested that the neurodegeneration-related changes and abnormality in morphology in substantia nigra seen in METH abusers are associated with increased risk of developing Parkinson's disease that results from loss of dopaminergic neurons. It has been also reported that METH causes neurotoxicity to other types of neurons including serotonergic, glutamatergic, GABAergic, and cholinergic neurons, suggesting that interactions between dopaminergic and the other neurotransmitter systems affects the behavioral and neuronal responses to METH.

3.2. Regulation of intracellular Ca^{2+} concentration via IP3Rs

Ca^{2+} is an intracellular second messenger controlling several cellular events. The intracellular Ca^{2+} concentration is tightly regulated from Ca^{2+} sources at the extracellular space and at the intracellular Ca^{2+} stores including ER and mitochondria. Ca^{2+} in the ER lumen is released via inositol 1,4,5-triphosphate receptors (IP3Rs), ryanodine receptors (RyRs), and polycystin-2 [91]. The Sig-1R has been shown to be involved in IP3Rs-mediated regulation of intracellular Ca^{2+} concentration ($(\text{Ca}^{2+})_i$). There are three different isoforms of IP3Rs: type 1 (IP3R1), type 2 (IP3R2), and type 3 (IP3R3). A predominant isoform usually exists in particular cellular types, for example, IP3R1 in neurons, IP3R2 in liver and heart, and IP3R3 in cultured cells. However, most types of cells express two or all of the three isoforms [92].

The Sig-1R agonist was reported to enhance bradykinin-induced elevation of $(\text{Ca}^{2+})_i$ most likely via IP3/IP3R3, which is in turn inhibited by the Sig-1R antagonist in neuroblastoma/glioma hybrid NG108 cells [93,94]. Later, it was demonstrated that the Sig-1R and IP3R3 are both enriched at the MAM, where the Sig-1R stabilizes IP3R3 when cells were either under ER stress due to the ER Ca^{2+} depletion or being stimulated by Sig-1R agonists; leading thus to the potentiation of Ca^{2+} transmission from ER to mitochondria [13].

While the IP3R3 has been proved as a client of the Sig-1R chaperone, it remains less clear if IP3R1 and IP3R2 are also chaperoned by the Sig-1R. Nevertheless, there are reports supporting the possibility that IP3R1 and IP3R2 are also clients of the Sig-1R chaperone. IP3R1 is enriched at the MAM in other cell types including HeLa cells and the rat liver tissue lysate [95]. As well, the Sig-1R is co-immunoprecipitated with IP3R1 in hepatocytes [96]. In the heart, IP3R2 contributes to the Ca^{2+} influx into mitochondria and the Sig-1R is physically associated with IP3R2. Interestingly, the Sig-1R stimulation by the agonists ameliorates cardiac hypertrophy and dysfunction through the enhancement of the Sig-1R-IP3R2 interaction and by

restoring the IP3R2-mediated Ca^{2+} mobilization from the ER into the mitochondria and the resultant mitochondrial ATP production [97,98]. Recently, it was suggested that the RyR is involved in the cardiac protective effects of Sig-1R agonists [98,99]. Therefore, the Sig-1R may regulate a variety of intracellular Ca^{2+} channels operated through both IP3Rs and RyRs, depending on the types of cells as well as the expression patterns of IP3R and RyR isoforms.

In agreement with previous studies [93,94], Barr et al. recently indicated that cocaine potentiates $(\text{Ca}^{2+})_i$ elevation through IP3Rs that are activated by inositol 1,4,5-triphosphate (IP3) and adenosine triphosphate (ATP) in dopamine D1 receptor (D1R) positive neurons in the NAc. The report showed that this effect of cocaine is not related to the extracellular Ca^{2+} [100]. This effect of cocaine is IP3R specific and not related to RyRs, which is abolished by pretreatment with Sig-1R antagonists. Further, cocaine alone did not cause the elevation of $(\text{Ca}^{2+})_i$. Interestingly, indirect activation of D1R by cocaine and amphetamine have been shown to augment IP3 levels in the striatum via phospholipase C [101]. Also, over expression of Sig-1R promotes mitochondrial Ca^{2+} uptake and ATP production [85]. In the study [100], cocaine was microinjected into cytoplasm, suggesting that cocaine directly activates the intracellular Sig-1R that stabilizes the IP3R function likely by chaperoning and causes thus the augmentation of ATP production. It was also showed that the increase of $(\text{Ca}^{2+})_i$ triggers activation of transient receptor potential canonical (TRPC) channels that allow for the activation of D1R positive neurons. Cocaine enhances the IP3Rs/TRPC-dependent depolarization through the Sig-1R and this pathway likely is involved in the cocaine-induced hyperactivity and sensitization since the cocaine effects are attenuated by pretreatment with the TRPC or Sig-1R inhibitor.

Recent studies suggest the involvement of IP3Rs in the development of drug dependence. IP3Rs antagonists dose-dependently inhibit the CPP induced by cocaine and METH. The IP3R1 expression level is elevated in the NAc of mice conditioned with those drugs. Further, the elevated IP3R1 is abolished by the selective antagonist for D1R or dopamine D2 receptors (D2R) [102,103]. One underlying mechanism for the upregulation of the IP3R1 expression is that stimulation of D1R and D2R, respectively, activates AP-1/NFATc4-dependent IP3R1 gene transcription [104,105]. This DA-dependent elevation of IP3R1 expression apparently is a key step to develop CPP induced by cocaine and METH.

Taken together, the above results suggest that during a CPP test cocaine or METH causes an indirect stimulation of D1R and D2R and the resultant upregulation of IP3R1 expression which may thus lead to the elevation of $(\text{Ca}^{2+})_i$. Interestingly, the Sig-1R mRNA and Sig-1R ligand binding activity in the NAc of cocaine-conditioned mice are concomitantly increased [106,107]. Thus, cocaine may

stimulate the Sig-1R chaperone activity at the ER, leading to the enhancement of the Ca^{2+} release via IP3Rs and the ultimate increase of ATP in the mitochondria. Sig-1R specific agonists alone are not sufficient to develop CPP. Yet, the DAT inhibitor-induced CPP is attenuated by Sig-1R antagonists [106], suggesting that the DA-dependent upregulation of IP3R1 might be critical for the Sig-1R's role in the acquisition of drug-induced CPP. Involvement of Sig-1R, IP3Rs, and D1R in the acquisition of CPP induced by cocaine is physiologically relevant since the antagonists for those receptors block the CPP [102,103,106,108,109,110]. The effect of Sig-1R antagonist on METH-induced CPP has not been reported so far.

3.3. Regulation of potassium channels

It has been documented that repeated cocaine treatment persistently decreases the intrinsic excitability of the NAc medium spiny neurons (MSNs) by increasing the outward K^+ current, leading to a long-lasting behavioral sensitization to cocaine. This process is believed to contribute to rewarding effects of cocaine and possibly to the development of the addictive processes to cocaine.

Cocaine-induced increase of K^+ current is postulated to be dependent on slowly-inactivating D-type (D-type) and SK-type Ca^{2+} -activated (SK) K^+ currents. Although modulation of SK channels by Sig-1R agonists has been reported [111], the recent study has clarified that the Sig-1R is involved specifically in the increase of D-type K^+ current mediated by chronic cocaine treatment [88]. The Sig-1R modulates D-type K^+ current through physical association with Kv1.2, one of K^+ channels through physical interaction. Cocaine increases the interaction between Sig-1R and Kv1.2 likely in the plasma membrane due to an increased Kv1.2 in the plasma membrane as a consequence of the activation and translocation of Sig-1R from the ER to the plasma membrane. This possibility is supported by the fact that protein expression levels of Sig-1R and Kv1.2 are not changed. Consistently, the Sig-1R antagonist and knockdown of Sig-1R prevent the cocaine-elicited increase of the D-type K^+ current and associated behavioral sensitization [88].

3.4. Regulation of gene transcription

It has been recognized that cocaine influences gene regulations that affect the neuronal plasticity and behavior. The nuclear envelope comprises two membranes called the inner and outer nuclear membranes and the Sig-1R has been detected in both membranes in retinal neurons [90]. In recent years, it has been revealed that nuclear envelopes play a role in chromatin organization and gene regulation [112]. Results of a recent study [113] demonstrated that the Sig-1R in the nuclear envelope is related to the cocaine-induced gene regulation. Upon cocaine stimulation, the

Sig-1R translocates to the nuclear envelope and, as a result, increases the interaction with nuclear envelope integral proteins lamin A/C and emerin. Cocaine intensifies the interactions between emerin, histone deacetylase (HDAC), and barrier-to-auto autointegration factor (BAF) in a Sig-1R-dependent manner. Emerin has been reported to affect epigenetic gene regulation through its binding to HDAC. BAF apparently assists emerin in the tethering of chromatin to the nuclear envelope. Cocaine thus utilizes the Sig-1R to promote the formation of a chromatin remodeling complex consisting of emerin/HDAC/BAF, and enhances its binding to the monoamine oxidase B (MAOB) promoter perhaps near the nuclear envelope. The nuclear periphery, where Sig-1R apparently forms the chromatin-remodeling complex, is somehow regarded as transcriptionally silent [112]. However, the Sig-1R knockdown increases the mRNA expression of MAOB [114] and this effect of the Sig-1R relates to its location and ability at the nuclear envelope [100]. Therefore, the Sig-1R at the nuclear envelope serves as the functional connection between the nuclear envelope and DNA. Thus, the stimulation of the Sig-1R by acute cocaine treatment causes the decreases of the MAOB protein expression via the suppression of the MAOB gene transcription in the prefrontal cortex and NAc in mice [100]. Together, those data indicate that the Sig-1R at the nuclear envelopes plays a role in the cocaine-mediated transcriptional downregulation of MAOB [113]. The MAOB is a DA degrading enzyme and is possibly involved in behavioral effects of cocaine. In fact, chronic pretreatment with a MAOB inhibitor prevents the establishment of cocaine self-administration [115]. Further, the MAOB inhibitor suppresses the prolonged behavioral sensitization induced by cocaine during cocaine-withdrawal [113]. However, the temporal pattern of the Sig-1R-related recruitment of chromatin-remodeling factors during the chronic cocaine treatment and after cocaine withdrawal remains to be fully clarified.

3.5. Regulation of reactive oxygen species signaling

Emerging evidence supports the possibility that the Sig-1R is involved in the generation of reactive oxygen species (ROS). It has been documented that the production of the NADPH-induced ROS is increased in the Sig-1R knockdown neurons [116]. Further, an elevated level of ROS is seen in the retinal Müller cells of Sig-1R knockout (KO) mice when compared to controls [117]. Additionally, the Sig-1R inversely regulates the ROS/nuclear factor kappa B ($NF\kappa B$)-dependent pathway. Thus, it was shown that the Sig-1R upregulates the Bcl-2 gene transcription in as much as the Bcl-2 transcription is downregulated by the ROS/ $NF\kappa B$ pathway [118]. Bcl-2 is a well-characterized antiapoptotic regulator and is also known to suppress autophagy by inhibiting Beclin 1, an autophagy inducing protein [119].

The ROS in cells is generated both in the mitochondria and ER, and the generation of ROS is affected by Ca^{2+} signaling and the converse is true. As mentioned before, the Sig-1R regulates the Ca^{2+} release from the ER and its influx to the mitochondria via IP3R3 [13]. As a consequence the Sig-1R may thus affect the mitochondrial ROS production. On the other hand, in Müller cells of Sig-1R KO mice, the expression of Nrf-2 gene, a transcriptional activator for antioxidant proteins, is downregulated, causing thus a decrease in antioxidant proteins such as SOD1, and catalase, as well as xCT that is important for generating the antioxidant glutathione [117]. Another potential mechanism might be related to the Sig-1R-induced downregulation of MAOB. Tyramine, an MAO substrate, induces the production of H_2O_2 , a ROS, which in turn could be inhibited by MAOA or MAOB inhibitor depending on the MAO isoforms expressed in the types of cells [120]. Collectively, the Sig-1R may control the ROS generation by regulating Ca^{2+} signaling from the ER into the mitochondria, and by regulating genes of ROS modulating factors such as SOD1, catalase, xCT, and MAOB. Further studies will be needed to fully elucidate the detailed mechanisms however.

Downstream of the ROS generated from mitochondria, there exists the IRE1 which is one of the ER stress sensors residing specifically at the MAM. Once activated, IRE1 causes the transcriptional upregulation of several ER chaperons in order to counteract the ROS-induced stress. In this mitochondrion-ER-nucleus signaling pathway, it is known that the Sig-1R chaperones IRE1 to maintain its proper folding, thus promoting the cellular survival [80]. Although evidence in terms of the Sig-1R's direct role in the generation or inhibition of ROS is lacking, indirect evidences mentioned above, including data from the Sig-1R knockdown and KO mice as well as the Sig-1R's cellular protecting function on the IRE1 downstream of the mitochondrial ROS, suggest that the Sig-1R apparently plays a protective role against the ROS insults under normal physiological conditions.

Previous reports have shown conflicting results regarding the effect of Sig-1R agonists and antagonists on the ROS generation. Sig-1R agonists increase the production of ROS and Sig-1R antagonists inhibit the agonist effect in the spinal cord and brain mitochondria [121,122]. On the other hand, a Sig-1R agonist, (+)-pentazocine, decreases ROS production induced by lipopolysaccharide (LPS) in retinal microglia [123]. Those results suggest that the Sig-1R agonist alone seems to enhance the ROS generation. However, this effect of the Sig-1R agonist may change depending on conditions for example when in the presence of other ROS inducers like LPS.

Yao et al. have indicated that the Sig-1R is directly involved in the cocaine effect on the ROS generation in microglia [124]. They postulated that cocaine induces the ROS generation by hijacking Sig-1Rs to the lipid raft at the

plasma membrane and sequentially activating the MAPKs, PI3K/Akt and $\text{NF}\kappa\text{B}$ pathways. Further, Sig-1R antagonist and knockdown of the Sig-1R attenuate the ROS production and the activation of those pathways. Additionally, this Sig-1R-mediated ROS induction is critical for cocaine to increase the monocyte chemoattractant protein-1 (MCP1) expression. MCP1 is the key CC chemokine to mediate monocyte-macrophage transmigration across the blood brain barrier (BBB). Consistently, cocaine enhances the monocyte migration into the brain in cocaine treated mice, an effect which is ameliorated by the Sig-1R antagonist. Thus, the Sig-1R-mediated ROS generation may explain at least in part how cocaine abusers with HIV-1 infection show a BBB disruption and a higher risk of neuroinflammation.

Acute and repeated cocaine administration have been described to induce the ROS production in the PFC and striatum in rats, an effect which is usually accompanied by increases of antioxidant enzymatic activities [125]. No significant apoptosis is observed probably because the activated antioxidant enzymes counteract the cocaine-induced oxidative stress. A very recent study has indicated that cocaine-induced ROS is involved in cocaine self-administration [126]. Pre- and post-treatment of ROS scavengers in the NAc reverses the cocaine self-administration without affecting food intake in rats. The report also found that the oxidative stress is activated mainly in neurons in cocaine self-administering rats, and that ROS scavengers suppress the cocaine-induced increase of DA in the NAc apparently without the involvement of dopamine transporter (DAT). Together, it is suggested that cocaine stimulates the ROS production in the NAc neurons that leads partly to the increase of DA and the subsequent expression of cocaine-self administration.

It has been demonstrated that Sig-1R antagonists alone do not affect the cocaine self-administration. Typical DAT inhibitors are known to shift the cocaine dose-effect curve to the left. However, combination of Sig-1R antagonists and DAT inhibitors decreases cocaine self-administration [127]. Underlying molecular mechanisms in this regard are largely unknown. Whether the Sig-1R-related ROS-dependent pathway may be involved in the self-administration of cocaine is also not known at present. Similar to cocaine self-administration, it has been reported that METH self-administration is attenuated by dual inhibition of DAT and sigma receptors [128].

Previous studies have provided evidence that the ROS signaling plays important roles in the effects of METH in vivo and in vitro. It was shown that METH increases the ROS production via various pathways [129,130] including the inhibition of mitochondrial functions [131] and the stimulation of the NADPH oxidase (NOX) activity [132]. METH-induced ROS production is implicated in METH

effects on neuronal degeneration [133,134], toxicity in various cell types [135,136], behavioral hyperactivity [137,138], and hyperthermia [139,140]. Notably, ROS-reducing agents including ROS scavengers and NOX inhibitors attenuate those effects of METH.

Specific involvement of the Sig-1R in the action of METH has been demonstrated in the METH-induced locomotor activity as well as in behavioral sensitization. Selective Sig-1R antagonists or Sig-1R antisense decrease the behavioral response caused by METH [22,141]. On the other hand, METH-induced ROS generation, apoptosis (at μM concentration), necrotic cell deaths (at mM concentration), or DA release is inhibited by subtype nonselective sigma antagonists in differentiated NG108-15 cells [142,143]. Interestingly, 1,3-di(2-tolyl)-guanidine (DTG), a sigma agonist, shifts the METH dose-response curve to the left in the METH-induced cell death. In mice, sigma antagonists block the METH-induced hyperthermia and damage in dopaminergic and serotonergic neurons as seen in the depletion of dopamine and serotonin, and the reduction of the transporters in the striatum in addition to blocking the locomotor activity and memory impairment caused by METH [144,145,146,147]. It should be mentioned that METH-induced hyperthermia apparently exacerbates the neuronal toxicity of METH [143,148]. The Sig-1R's specific role in the molecular mechanism underlying the METH-induced effects is unknown at present. However, it is conceivable that the Sig-1R may play a role in the neuronal and behavioral effects of METH by regulating the ROS signaling.

3.6. Regulation of autophagy

Autophagy is a lysosomal degradation pathway responsible for the turnover of cellular organelles and larger protein aggregates whose sizes are beyond that the proteasome can handle. The autophagy process includes the sequestration of cytoplasmic components within a double-membrane compartment (autophagosome) and the subsequent fusion of autophagosome with lysosomes, followed by degradation. Autophagy can be prosurvival and prodeath depending on the cellular types and conditions.

Recently, a couple of studies have demonstrated the involvement of the Sig-1R in the process of autophagy. Knockdown of the Sig-1R impairs the fusion between autophagosome and lysosomes, thus leading to the accumulation of autophagosome. The accumulation of autophagosome is implicated in ALS, one of Sig-1R-related neurodegenerative disease [86]. Cao et al. recently demonstrated the cocaine-induced autophagy and suggested that the Sig-1R plays a role in the cocaine-induced autophagy in a mammalian target of rapamycin (mTOR) and Beclin-1-dependent manner in astrocytes which are the most abundant cell type in the brain that supports

neuronal survival. The report showed that the knockdown of Sig-1R or a Sig-1R antagonist attenuates the cocaine-induced autophagy [149]. Cocaine-induced autophagy causes the apoptosis-independent cell death and may thus be implicated in the neuronal toxicity of cocaine.

It has been reported that cocaine is capable of stimulating inflammatory responses in the CNS by activating microglia. In response to prolonged exposure to cocaine, activated microglia produces cytokine, chemokine, and neurotoxic factors that can cause neuronal damage and dysfunction. A recent study showed that autophagy is involved in the cocaine-induced activation of microglia. Cocaine mediates the ROS production and ER stress whereby inducing autophagy that stimulates the production and secretion of proinflammatory factors in microglial cells. Indeed, induction of autophagy by cocaine is indicated by increased levels of autophagy markers, BECN1, ATG5, and MAP1LC3B-II, in the brain of mice repeatedly treated with cocaine [150]. Thus, the cocaine-induced ROS generation leads to autophagy that activates microglia. Whether the cocaine-induced microglial activation may involve the Sig-1R is unknown at present.

METH-induced autophagy is often tested in dopaminergic neurons because the disruption of dopaminergic system is a key effect of METH. Micromolar concentrations of METH, which do not kill cells, induce autophagy to protect cells from apoptosis [151,152]. This autophagy as such is speculated as an early cellular response to METH intoxication. High concentrations (mM) of METH, however, induce autophagy in a ROS-dependent manner, leading to the activation of apoptosis and cell death [153,154,155]. Thus, the moderate induction of autophagy by nontoxic concentration of METH is prosurvival whereas excess METH activates the autophagy that kills cells. Sigma antagonists have been shown to be protective against the METH-induced neuronal damage in vivo and in vitro [144,145,146,147]. Thus, the Sig-1R may participate in the METH-induced neuronal damages by the Sig-1R's ability to regulate autophagy via mechanisms as mentioned above.

4. Conclusions

The exact molecular mechanisms of actions of psychostimulants remain largely unknown even though behavioral and pharmacological studies have rapidly advanced in this field. As such, there is no effective medication against psychostimulant-related disorders at present. It is apparent that targeting monoamine systems alone may not be enough to develop effective treatments. The Sig-1R has been implicated in the actions of psychostimulants including cocaine and METH and is expected to be a potential target for treatment development.

The Sig-1R has a wide variety of functions in the cell. Those functions regulated by the Sig-1R include the protein

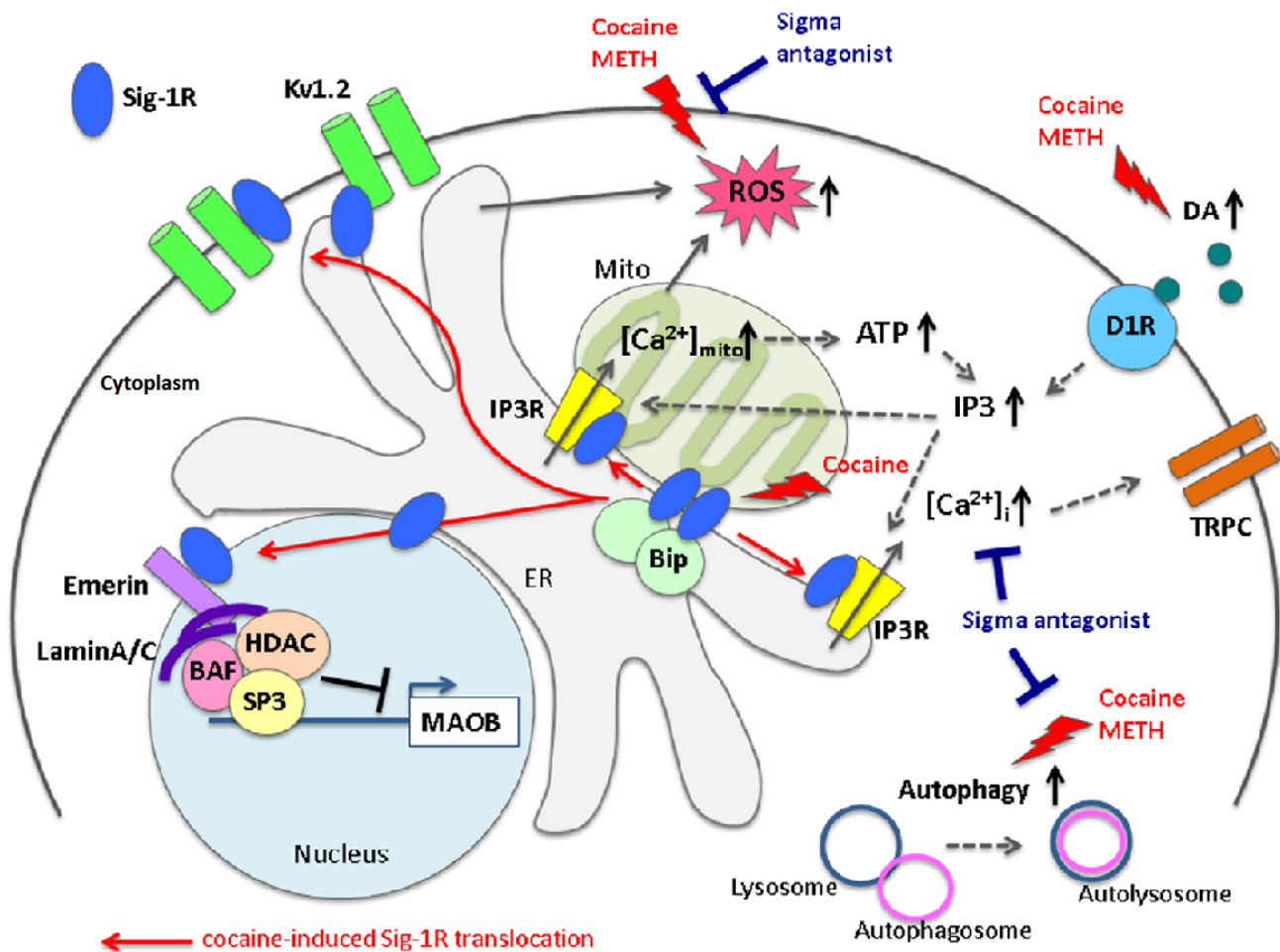


Figure 3: Potential Sig-1R-involved molecular mechanisms in the actions of cocaine and METH. Cocaine dissociates Sig-1R from Bip/GRP78 and activates the chaperone activity of Sig-1R. Sig-1R stabilizes IP3R leading to the increase of intracellular calcium concentration. Cocaine induces the translocation of Sig-1R from ER to the plasma membrane and the nuclear envelope, thus intensifying Sig-1R interaction with target proteins. At the plasma membrane, Sig-1R modulates the function of potassium channels by interacting with Kv1.2 subunit. At the nuclear envelope, cocaine through Sig-1R can promote the formation of the chromatin remodeling complex composed of emerlin/HDAC/BAF that binds to suppress the gene transcription of MAOB. Cocaine or METH induces the ROS production and autophagy which can be inhibited by sigma receptor antagonists. Abbreviations: ER, endoplasmic reticulum; Mito, mitochondria; DA, dopamine; D1R, dopamine D1 receptor; TRPC, transient receptor potential canonical; IP3, inositol 1,4,5-triphosphate; IP3R, IP3 receptor; ROS, reactive oxygen species; ATP, adenosine triphosphate; BAF, barrier-to-auto autointegration factor; HDAC, histone deacetylase; MAOB, monoamine oxidase B; $[Ca^{2+}]_i$, intracellular Ca^{2+} concentration; $[Ca^{2+}]_{mito}$, mitochondrion Ca^{2+} concentration.

stability, intracellular Ca^{2+} signaling, gene transcription, ER and oxidative stress signaling, protein degradation by the ER-associated protein degradation, and autophagy. In turn, those cellular functions could be affected by cocaine and METH via the involvement of the Sig-1R, eventually leading to functional alterations or damage in the cell.

It has been suggested that the Sig-1R may relate to the abuse of ethanol and nicotine. Although the Sig-1R itself does not bind ethanol or nicotine, the Sig-1R ligands modulate behavioral responses to ethanol and nicotine. Perhaps the Sig-1R may indirectly participate in the

addictive processes of ethanol or nicotine in a manner which has yet to be unveiled.

In summary, the exact roles of the Sig-1R in the actions of psychostimulants or other abused substances await to be fully understood (Figure 3). Understanding the mechanism of actions for the Sig-1R in its full spectrum will certainly advance our understanding of this unique receptor and its exact roles in the actions of cocaine and METH in particular, but perhaps also other substances of abuse as well.

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Conflict of interest The authors declare that they have no conflict of interest.

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