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When the Endogenous Hallucinogenic Trace Amine *N*,*N*-Dimethyltryptamine Meets the Sigma-1 Receptor

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Abstract

N,*N*-dimethyltryptamine (DMT) is a hallucinogen found endogenously in human brain that is commonly recognized to target the 5-hydroxytryptamine 2A receptor or the trace amine–associated receptor to exert its psychedelic effect. DMT has been recently shown to bind sigma-1 receptors, which are ligand-regulated molecular chaperones whose function includes inhibiting various voltage-sensitive ion channels. Thus, it is possible that the psychedelic action of DMT might be mediated in part through sigma-1 receptors. Here, we present a hypothetical signaling scheme that might be triggered by the binding of DMT to sigma-1 receptors.

Some amino acid metabolites are biogenic amines that, unlike the major neurotransmitter amines, such as dopamine, nore-pinephrine, and 5-hydroxytryptamine (5-HT), are typically present at low concentrations and accumulate in high amounts only if the amine-digestive enzyme monoamine oxidase is inhibited. These trace amines (TAs) include β-phenylethylamine, tyramine, octopamine, synephrine, and tryptamine, as well as some of their metabolites or derivatives. TAs are purported to be involved in several human diseases (1). Here, we focus on findings related to *N*,*N*-dimethyltryptamine (DMT), a tryptamine metabolite with psychedelic effects. DMT is the main ingredient in the hallucinogenic beverage called “ayahuasca,” which has been brewed (by boiling the bark of *Banisteriopsis caapi* together with the leaves of *Psychotria viridis*) and used by indigenous people around the South American Amazon basin (2, 3). Using purified DMT, Szara and colleagues first reported the psychoactive effect of the compound in humans (4, 5). Saavedra and Axelrod then demonstrated the formation of DMT in rat and human brain (6), leading both groups to propose that DMT was an endogenous hallucinogen (4–6). Several studies have since confirmed the psychedelic properties of DMT in humans (7–14).

DMT is generally believed to exert its psychedelic effects through the 5-HT receptor, specifically the 5-HT2A subtype, which was identified by using the semisynthetic hallucinogen lysergic acid diethylamide (LSD) (15). However, certain behaviors seen in rats treated with DMT (0.5 to 35 mg/kg administered intraperitoneally), such as jerking, retropulsion, and tremor, do not involve the 5-HT system or other monoaminergic systems (16). Micro-molar concentrations of DMT enhances phosphatidylinositol production in a

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manner that is not blocked by the 5-HT2A receptor antagonist ketanserin (17), which suggests that part of the action of DMT is not mediated through 5-HT receptors. With the discovery of the G protein–coupled TA-associated receptors (TAARs), which activate adenylyl cyclase and cause cyclic adenosine monophosphate (cAMP) accumulation (18, 19), it was speculated that TAARs mediated part of the pharmacological or psychedelic effect of trace amines, including DMT, as well as LSD. (19). Although DMT at 1 μM is as potent in eliciting cAMP accumulation as the prototypic trace amine tryptamine or LSD (19), it is unclear whether TAARs mediate the psychedelic effect of trace amines, including DMT, because TAAR antagonists have not been tested in humans in this regard. Furthermore, gene association studies attempting to link TAARs and psychiatric disturbances have generated conflicting results as to whether TAARs are involved in schizophrenic symptomatologies, including hallucination. *TAAR1* knockout mice display a deficit in “prepulse inhibition” (PPI), or the ability to suppress the magnitude of startle induced by an incoming acoustic signal that had been previously experienced (20). They are therefore a relevant animal model for schizophrenia because the PPI is typically impaired in schizophrenic patients (20). In addition, a genetic study has demonstrated associations between polymorphisms in the TAAR4 subtype with susceptibility to schizophrenia (21); however, conflicting reports later emerged that demonstrated a lack of association between the *TAAR4* or *TAAR6* gene and schizophrenia (22, 23). Thus, it remains to be fully established whether TAARs mediate the psychotomimetic action of DMT.

A report now demonstrates that DMT targets a receptor called the sigma-1 receptor (Sig-1R) (24). DMT binds to the Sig-1R with a moderate affinity at about 14 μM (24). Although this affinity is not impressive when compared to other Sig-1R ligands, such as (+)pentazocine (which has an affinity in nanomolar range), high concentrations of DMT (100 μM, about 7 times as high as its affinity for Sig-1R) could nonetheless inhibit voltage-gated sodium channels (24), a hallmark action of Sig-1R ligands and Sig-1Rs (25). Sig-1R knockout mice, which reacted normally to the locomotor stimulating effect of methamphetamine, did not become hyper-active in response to DMT (24), a phenomenon also observed with the prototypic Sig-1R agonist *N*-allylnormetazocine, an opiate analog better known as SKF-10047 (26). Furthermore, the locomotor-stimulating action of DMT resembles that of SKF-10047 (24, 26). These results definitively link the action of DMT to the Sig-1R.

The Sig-1R was originally thought to be the opiate receptor subtype that mediated the psychotomimetic or drug-induced psychotic-like effect of SKF-10047 in animals (27). However, the same laboratory later found that the psychotomimetic effect of SKF-10047 was not reversed by naloxone, a universal antagonist for all opiate receptor subtypes (28). Thus, the Sig-1R was recognized to be a nonopiate receptor (29–31) that might mediate the psychotomimetic effect not only of SKF-10047 but also of the dissociative anesthetic phencyclidine (PCP) (28, 32). However, PCP is thought to induce its mind-altering effect through the *N*-methyl-D-aspartate (NMDA) receptor, and systematic behavioral studies are needed to differentiate between the SKF-10047– and PCP-induced effects mediated by the Sig-1R versus the NMDA receptor. In addition to their postulated psychotomimetic action, Sig-1Rs have been implicated in diseases such as addiction, depression, amnesia, pain, stroke, and cancer (33).

Sig-1Rs localize at the interface between the endoplasmic reticulum (ER) and mitochondrion, which is known as the mitochondria-associated ER membrane (MAM). Sig-1R agonists at affinity concentrations (i.e., close to their K_i values) cause Sig-1Rs to disassociate from another ER chaperone, binding immunoglobulin protein (BiP), allowing them to act as molecular chaperones to inositol 1,4,5-trisphosphate (IP_3) receptors. By stabilizing IP_3 receptors, Sig-1Rs at the MAM enhance Ca^{2+} signaling from the ER into mitochondria (34, 35), thereby activating the tricarboxylic acid (TCA) cycle and increasing

the production of adenosine triphosphate (ATP) (35) (Fig. 1). Although Sig-1Rs reside primarily at the ER, they can translocate from the MAM to the plasma membrane (also termed the plasmalemma) or the subplasma membrane area when stimulated by higher concentrations (e.g., at approximately 10-fold K_i) of Sig-1R ligands or when Sig-1Rs are overexpressed in cells (36–38) (Fig. 1). This may explain why higher concentrations of Sig-1R ligands result in the inhibition of various ion channels at the plasma membrane and, in particular, why the channel-inhibiting concentration of DMT is almost 10 times as high as its affinity concentration (24). By triggering the translocation of Sig-1Rs from the MAM to the plasma membrane or subplasma membrane, high concentrations of Sig-1R ligands may allow Sig-1Rs to directly interact with and inhibit channel proteins (24, 38). High concentrations of Sig-1R ligands tonically inhibit the small conductance K^+ (SK) channel, which in turn leads to the potentiation of NMDA receptors (39). The $Na_V1.5$ channel (24, 25), the $K_V1.4$ channel (38), the voltage-gated N-, L-, and P/Q-type Ca^{2+} channels (40), the acid-sensing ion channel (41), and the volume-regulated Cl^- channel (42) are also inhibited by high concentrations of Sig-1R ligands.

So, do sigma-1 receptors mediate the psychedelic effect of DMT? First, we need to specify that Sig-1Rs have not been firmly established as being involved in causing psychotomimesis. Secondly, moderate concentrations of selective Sig-1R ligands, including (+)pentazocine and PRE-084, are not reported to cause psychotomimetic-like effects in animals (43). However, the possibility that Sig-1Rs are involved in psychotomimesis cannot be totally excluded at present. We therefore speculate that Sig-1Rs may partially mediate the psychotomimetic effects of DMT, such as visual hallucinations in humans (7–14). PCP and SKF-10047 cause animals to behave as if they are hallucinating (they move their heads and eyes as if they are tracking objects in the air) (28). Could the psychotomimetic effect caused by PCP and SKF-10047 in animals (28) be explained by PCP or SKF-10047 blocking NMDA receptors and not by their binding to Sig-1Rs? It might not be, because it might be difficult to distinguish the psychedelic effect mediated by the NMDA receptor blockade from that mediated by Sig-1Rs in animal studies. A clearer differentiation of the effects mediated by the two different receptors might come only from human studies. Results from previously mentioned clinical studies, although not designed to answer this question, might provide some interesting clues.

DMT, which we know now is also a Sig-1R ligand, has been used as a 5-HT2A agonist by Gouzoulis-Mayfrank *et al*. to compare the psychedelic effect of DMT with that of ketamine, which is also an NMDA receptor blocker like PCP (11–14). DMT effects relate more to the paranoid-type psychoses with particular positive formal thought disorders—including loosening of associations, derailment, and distractibility—than to the neurocognitive impairment seen with ketamine (11, 14). Thus, DMT effects in humans might be mediated through Sig-1Rs or 5-HT2A receptors and not through blockade of NMDA receptors. In this regard, it would be interesting to examine whether Sig-1R antagonists block the psychedelic effect of DMT in humans.

Based on the current understanding of the cell biological actions of Sig-1Rs (34, 35, 38), we propose a hypothetical scheme for the molecular mechanism by which DMT signals through sigma-1 receptors (Fig. 1). Like other Sig-1R agonists (34), DMT at affinity concentrations (14 μM) (24) might cause the dissociation of Sig-1Rs from the Sig-1R-BiP complex (34, 35) (Fig. 1A), and at higher concentrations (100 μM) (24) might cause Sig-1Rs to translocate from the MAM to the plasma membrane (36, 37) (Fig. 1B). By doing so, DMT might first unleash the chaperone activity of the free form of Sig-1Rs at the MAM (34) and then cause the receptors to translocate (36, 37) to the plasma membrane to inhibit voltage-gated ion channels (24, 38–42). We do not know at present whether the chaperone activity of Sig-1Rs contributes to ion channel inhibition or whether Sig-1Rs associate with ion channels at the

subplasma ER membrane or at the plasma membrane. Nor do we know whether the chaperone-unleashing action seen at affinity concentrations of DMT or the ion channel–inhibiting action caused by high concentration of DMT relate to the psychedelic effect induced by DMT. More studies are needed to provide answers to these questions.

Almost 30 years after the initial description of a psychotomimesis-related sigma receptor (27–32), investigators have identified DMT as an endogenous hallucinogen that targets a new site of action (24). The characterization of Sig-1Rs as ligand-regulated chaperone receptors (34) and the discovery of the endogenous hallucinogen DMT as a Sig-1R ligand (24) represent potential breakthroughs in drug abuse research. Yet many questions remain, the most important being: What is the physiological importance or relevance of the DMT signaling through Sig-1Rs? Furthermore, Sig-1Rs are present not only in the central nervous system, but also in peripheral organs such as the liver, heart, lung, adrenal gland, spleen, and pancreas (34). For example, the enzyme that synthesizes DMT from its precursor tryptamine (44) and Sig-1Rs (34) are particularly abundant in lung tissue. Thus, it will be important to delineate the roles of Sig-1Rs and their associated ligands, including DMT, within the context of the physiology or pathophysiology of human diseases related to those organs. It is hoped that future research will increase our understanding of these roles.

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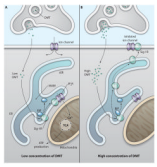

Fig. 1.

Hypothetical scheme illustrating the signaling of *N*,*N*-dimethyltryptamine through sigma-1 receptors. (**A**) Sigma-1 receptors (Sig-1Rs) at the mitochondrion-associated endoplasmic reticulum (ER) membrane (MAM) function as ligand-activated molecular chaperones, particularly when ligands are present at concentrations close to their affinities (34). Sig-1R ligands, including DMT, at concentrations close to their K_i values, cause the dissociation of Sig-1Rs from another ER chaperone, binding immunoglobulin protein (BiP) (34), allowing Sig-1Rs to chaperone inositol 1,4,5-trisphosphate receptors (IP_3Rs) at the MAM (34). This enhances Ca^{2+} signaling from the ER into mitochondria (34, 35), activates the tricarboxylic acid (TCA) cycle, and increases adenosine triphosphate (ATP) production (35). (**B**) Higher concentrations of DMT cause the translocation of Sig-1Rs from the MAM to the plasma membrane, leading to the inhibition of ion channels. Thus, Sig-1R ligands might shift the site of action of Sig-1R chaperones from the center of the cell to its periphery. In the present scheme, Sig-1Rs and related molecules or organelles are illustrated in the postsynaptic region for the sake of simplicity, although they may also be present presynaptically or in glia.