

Dimethyltryptamine: Possible Endogenous Ligand of the Sigma-1 Receptor?

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How likely is it that ability of DMT to activate the sigma-1 receptor actually contributes to its hallucinogenic effects?

N,N-dimethyltryptamine, commonly known as DMT, is a member of the serotonergic class of hallucinogens, which includes compounds such as LSD, mescaline, and psilocybin. DMT was first synthesized in 1931 [1], but was later shown to be a naturally occurring constituent of a wide variety of plant species. Several of those plants, such as *Psychotria viridis* and *Anadenanthera peregrina*, have traditionally been employed as hallucinogens by native populations of South America. The first human studies with synthetic DMT were conducted by Steven Szára in the mid-1950s, and those studies demonstrated that DMT produces effects resembling those induced by LSD and mescaline [2]. More recent laboratory studies with intravenous DMT have extensively characterized the psychological and physiological effects of DMT in human volunteers [3,4]. As with other serotonergic hallucinogens, it is currently accepted that the subjective effects of DMT are mediated primarily by activation of 5-HT_{2A} serotonin receptors [5,6]. Interestingly, there has been some speculation that DMT may be a normal constituent of the human brain, and may be involved in dreaming [7], near-death experiences [8], and schizophrenia [9].

Although normally a relatively obscure hallucinogen, DMT has recently received an unusual amount of attention in the mainstream scientific press. The reason for the focus on DMT is the publication of a report in the journal *Science* proposing that DMT is the endogenous ligand for the sigma-1 receptor [10]. The three main findings of the *Science* article are that DMT binds to the sigma-1 receptor with moderate affinity (albeit with much lower affinity than for the 5-HT_{2A} receptor and other 5-HT receptors), that binding of DMT to the sigma-1 receptor causes inactivation of a voltage-gated sodium channel, and that deletion of the gene coding for the sigma-1 receptor abolishes one aspect of the behavioral response to DMT in mice. These findings are very intriguing, and do suggest that the interaction of DMT with the sigma-1 receptor is worthy of further study. Nevertheless, the report raised two questions in my mind: (1) How convincing is the evidence that DMT is actually present endogenously in the brain; and (2) how likely is it that the ability of DMT to activate the sigma-1 receptor actually contributes to its hallucinogenic effects?

Is DMT an endogenous signaling molecule in the brain?

Although it may seem surprising that a plant compound such as DMT could also serve as a transmitter in the brain, the finding is not without precedent. Indeed, morphine may itself be an endogenous brain chemical [11]. DMT has been proposed to be present endogenously in animals and humans based on two types of evidence: (1) the discovery of an enzyme (indoleethylamine N-methyltransferase, INMT) in several species of mammals that is capable of synthesizing DMT; and (2) analytical studies that have directly detected DMT in tissues, blood, and urine. In 1961, Julius Axelrod isolated an enzyme from rabbit lung that can convert tryptamine (a compound derived from the amino acid tryptophan that is normally present in the body) and N-methyltryptamine to DMT by transferring methyl groups from S-adenosylmethionine (SAM) [12]. It was subsequently shown that a similar enzyme exists in the brains of chicks, sheep, rats, and humans [13-16]. Two groups also demonstrated that injection of tryptamine directly into the brains of rats leads to the production of small amounts of DMT, suggesting that tryptamine can be biotransformed to DMT in vivo [15,17].

Despite those findings, other workers reported that although they could detect N-methyltransferase activity in peripheral tissues, they were unable to confirm that the enzyme was present in the brain [18,19]. A possible explanation for these discrepant findings soon emerged when it was shown that incubation of red blood cells or rat brain extracts with SAM and N-methyltryptamine produces tetrahydro-beta-carbolines (THBCs) almost exclusively, and very little DMT [20,21]. It turned out that many of the DMT biosynthesis studies had isolated DMT using a technique known as thin layer chromatography (TLC), and under certain conditions it is very difficult to distinguish THBCs from DMT using TLC. It was concluded that the brain actually contains very little INMT, but it does contain enzymes that are capable of converting SAM to formaldehyde, which can then react nonenzymatically with tryptamines to yield beta-carbolines. More recently, Thompson and colleagues were able to clone the genes that encode rabbit and human INMT [22,23], and these and other studies confirmed that INMT is expressed in lung and other peripheral tissues but is not expressed at appreciable levels in the brain.

There is evidence that DMT is present in the peripheral tissues of rats and humans [24], which is not surprising given that INMT is expressed peripherally. What is less clear is whether DMT occurs endogenously in the

central nervous system. Very low levels of DMT have been detected in the brains of rats [24]. I am not aware of any studies that have detected DMT in the human brain, but DMT has been shown to occur in the cerebrospinal fluid of human volunteers [25]. INMT is expressed in the spinal cord [23], and this is one possible source for DMT in cerebrospinal fluid. Additionally, there is evidence that DMT may accumulate in the brain by uptake from the circulatory system [26-28]. There is, however, some controversy regarding whether DMT occurs endogenously in human blood [29,30]. Importantly, a recent study using a highly sensitive and selective detection method failed to detect the presence of DMT in whole blood or plasma from human volunteers [24].

Traditionally, in order to be classified as a neurotransmitter or neuromodulator, a substance had to meet three criteria: it must be present within neurons, it must be released upon neuronal depolarization, and there must be receptors for the substance. Morphine, for example, appears to meet all three criteria. Morphine has been shown to be present within neurons in specific brain regions [31,32], and is released by neurons after depolarization [33]. Furthermore, there is evidence that morphine is synthesized in the brain [34]. By contrast, although DMT may be present in the brain in small amounts, it is probably not synthesized locally, and there is little evidence that it is localized within neurons or is released when they are depolarized. This observation calls into question whether DMT actually acts as a signaling molecule in the brain, as opposed to existing as an artifact of peripheral biosynthetic pathways. Clearly, there is currently little evidence to support the contention that DMT functions as a neurotransmitter or neuromodulator.

Does the sigma-1 receptor contribute to the hallucinogenic effects of DMT?

DMT is unquestionably present in peripheral tissues, and it is possible that it may be an endogenous ligand of sigma-1 receptors in the periphery. However, in light of the evidence outlined above, it is unlikely that DMT is an endogenous ligand for sigma-1 receptors in the brain. This conclusion does not preclude the possibility that the action of DMT at sigma-1 receptors may contribute to the hallucinogenic effects of the drug.

The existence of the sigma-1 receptor was first proposed in 1976 to explain the hallucinogenic effects of a class of opioids known as the benzomorphans [35]. Certain benzomorphans, such as the analgesics pentazocine and cyclazocine, produce hallucinogenic effects

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when administered to humans, and these compounds activate the sigma-1 receptor. It was later shown in clinical trials that the hallucinogenic effects of the benzomorphans are prevented by naloxone [36,37], which blocks opiate receptors but not sigma-1 receptors. Thus, it is currently accepted [38] that the hallucinogenic effects of the benzomorphans are mediated by the kappa-opioid receptor—the same receptor that is responsible for the effects of the hallucinogen salvinorin A from the plant *Salvia divinorum*. Thus, there is very little evidence linking the sigma-1 receptor to hallucinogenic effects. In fact, many drugs that activate the sigma-1 receptor, such as cocaine and certain steroid hormones, are not hallucinogenic.

One area that needs to be investigated is whether administration of DMT actually results in brain concentrations that are sufficient to activate the sigma-1 receptor. The reported disassociation constant of DMT for the sigma-1 receptor (14.75 μM , see [10]) is several-fold higher than the plasma concentrations of DMT that occur after intravenous administration of a high dose of the drug to humans (0.17–1.08 μM , see [3]). By contrast, the affinity of DMT for 5-HT_{2A} receptors in the human cortex is reportedly 462 nM [39], which matches up very closely with the plasma concentrations of DMT reported by Strassman and Qualls [3]. It should be noted that there is some evidence that DMT may actively accumulate in the brain [26-28], making it possible that the concentration of DMT in the brain may be higher than the plasma concentration. Nevertheless, even if DMT brain levels are several-fold higher than plasma concentrations, it is still not clear that the concentration of DMT in the brain would be high enough to produce substantial activation of sigma-1 receptors. A photolabeling protection study of the sigma-1 receptor (a method

used to measure the degree of occupation of the receptor by DMT) demonstrated that less than 50% of sigma-1 receptors are occupied by 50 μM DMT [10].

Based on the above evidence, it is likely that the concentration of DMT required to induce effects via the sigma-1 receptor would produce extremely high levels of 5-HT_{2A} receptor occupation. It is well-established that the 5-HT_{2A} receptor is responsible for mediating the effects of psilocybin and other hallucinogens [6]; thus, in all probability the hallucinogenic effects of DMT are mediated by the 5-HT_{2A} receptor and not by the sigma-1 receptor. There is, however, one possible linkage between 5-HT_{2A} receptors and sigma-1 receptors. One effect of 5-HT_{2A} receptor activation is the production of inositol-1,4,5-triphosphate within neurons, which leads to elevated intracellular levels of calcium. The sigma-1 receptor has been shown to associate with the receptor for inositol-1,4,5-triphosphate and regulate calcium signaling [40]. It is thus theoretically possible that the 5-HT_{2A}-mediated effects of DMT could be modulated by the action of the drug at sigma-1 receptors. Further studies are necessary to determine whether the interaction with sigma-1 receptors contributes to or modifies the psychoactive effects of DMT. In conclusion, although it would be very interesting to find that a hallucinogen such as DMT acts as a neuromodulator, given the available evidence it seems unlikely that DMT is an endogenous signaling molecule in the human brain. Furthermore, there is little evidence to support the hypothesis that the sigma-1 receptor is responsible for mediating the hallucinogenic effects of DMT. •

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