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Endogenous hallucinogens as ligands of the trace amine receptors: A possible role in sensory perception

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SUMMARY

While the endogenous hallucinogens, *N*,*N*-dimethyltryptamine, 5-hydroxy-*N*,*N*-dimethyl-tryptamine and 5-methoxy-*N*,*N*-dimethyltryptamine, have been acknowledged as naturally occurring components of the mammalian body for decades, their biological function remains as elusive now as it was at the time of their discovery. The recent discovery of the trace amine associated receptors and the activity of DMT and other hallucinogenic compounds at these receptor sites leads to the hypothesis that the endogenous hallucinogens act as neurotransmitters of a subclass of these trace amine receptors. Additionally, while activity at the serotonin 5-HT_{2A} receptor has been proposed as being responsible for the hallucinogenic affects of administered hallucinogens, in their natural setting the 5-HT_{2A} receptor may not interact with the endogenous hallucinogens at all. Additionally 5-HT_{2A} agonist activity is unable to account for the visual altering effects of many of the administered hallucinogens; these effects may be mediated by one of the endogenous hallucinogen trace amine receptors rather than the serotonin 5-HT_{2A} receptor. Therefore, activity at the trace amine receptors, in addition to serotonin receptors, may play a large role in the sensory altering effects of administered hallucinogens and the trace amine receptors along with their endogenous hallucinogen ligands may serve an endogenous role in mediating sensory perception in the mammalian central nervous system. Thus the theory proposed states that these compounds act as true endogenous hallucinogenic transmitters acting in regions of the central nervous system involved in sensory perception.

Introduction

N,*N*-Dimethyltryptamine (DMT), 5-hydroxy *N*,*N*-dimethyltryptamine (bufotenine) and 5-methoxy-*N*,*N*-dimethyltryptamine (5-MeO-DMT) have long been accepted as naturally occurring components of human blood, brain and cerebral spinal fluid [1,23,27,28]. While their biological presence is acknowledged, the biological function of the endogenous hallucinogens remains a mystery. One possibility, which has yet to be formally proposed, is that these compounds act as formal neurotransmitters of the central nervous system (CNS) and exert a signaling function in regions of the CNS which are involved in sensory perception. The 2001 discovery of the trace amine associated receptor (TAAR) family [2,3] and the activity of several hallucinogens including DMT, at these receptor sites [24] supports the existence of these compounds as neurotransmitters of the TAARs. Members of the TAAR family have been shown to be expressed throughout the CNS, including areas important to sensory perception including the prefrontal cortex, hippocampus, substantia nigra, amygdala and basal ganglia [2,9]. Currently nine TAAR genes have been observed in humans [29].

In vitro pharmacological studies have shown that several TAAR subtypes respond to trace amines other than the classical trace amines; *p*-tyramine, β-phenethylamine, tryptamine and octopamine [29]. This suggests the occurrence of additional endogenous TAAR ligands such as DMT, 5-MeO-DMT, bufotenine and possibly others. The role of the trace amine (TA) system in humans is currently under debate. Interestingly, trace amines have been shown to mediate sensory perception in insects [4–6]. While this does not imply the trace amines serve an analogous function in mammals it is never the less intriguing. Additionally insects may represent a new opportune organism for behavioral studies into the perceptual altering abilities of these compounds. It is likely that the TAARs play a role in numerous neural processes. Genetic studies have associated alterations in the TAAR gene family with schizophrenia [7–9] and other CNS disorders such as bipolar disorder [8]. Additionally it has been shown that a specific mutation in the TAAR6, previously TAAR4, gene TRAR4 has been correlated most significantly with the delusional and hallucinogenic symptoms of schizophrenia [7]. This implicates TRAR4 as being expressed in neural regions involved in sensory perception. Therefore, it is not surprising that TAAR6 is found in several key sensory processing brain regions including the amygdala, the hippocampus and the frontal cortex [9]. As TAAR6's endogenous ligand is unknown, it may be one of the endogenous hallucinogens.

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The exhaustive legal restrictions placed on these simple biological compounds have severely limited their availability for scientific research. These restrictions are based on socio-political motives rather than sound scientific basis. Hopefully the acknowledgement of these compounds as true neurotransmitters of the CNS will lead to a new found appreciation of their medical value. A thorough understanding of the activity of these compounds within the CNS will lead to novel treatments for psychological disorders as well as to an understanding of the neurochemistry of sensory experience. The areas of the CNS where administered hallucinogens act play a role in sensory perception and it is for this reason that these compounds exert their complex perceptual altering abilities.

DMT endogenous role as a neurotransmitter

Jacob and Presti have proposed an anxiolytic role for endogenous DMT [11]. This theory is based on the reported subjective effects of low dose DMT administration in normal human volunteers [12] and the belief that these low dose administrations are comparable in concentration and biological action to endogenous DMT [11]. The trouble in drawing this type of conclusion is that it is only appropriate if the compound of interest acts as a hormone and not a neurotransmitter. If DMT is indeed a neurotransmitter of the TAARs and not a hormone, then endogenous DMT would unlikely exert any effect on 5-HT receptors but would rather act at its endogenous TAAR. However, low levels of administered DMT would still act as an agonists at 5-HT receptors, in fact due to large differences in the concentrations of 5-HT receptors relative to TA receptors, it can be argued that any subjective responses from low dose DMT administration would result from 5-HT rather then TA activity. It may be only when high concentrations of DMT are administered that a significant number of TAARs are activated, leading to a TAAR mediated response. The role of DMT as a true endogenous hallucinogen at the TAAR sites is strengthened by the fact that the sensory alterations occur only when relatively high concentrations of DMT are administered; these high concentrations would be similar to those observed in the synapse when endogenous DMT is released.

The goal of a neurotransmitter is opposite that of a hormone. A transmitter acts on a sub-population of possible receptors in a localized manner whereas a hormone acts indiscriminately on all sites it is capable of binding to (affinity considered). With neurotransmitters, complex computations are able to be carried out in isolated regions of the CNS. The transmitter is released from the presynaptic terminal and then has a localized effect at the postsynaptic receptors on glial and neural cells. The transmitter is then quickly removed from the synapse clearing the way for the flow of new chemical information. A small portion of the transmitter diffuses into the plasma where it is able to have a delocalized effect on other receptors. Generally these concentrations are kept low by catabolic enzymes and transport mechanisms, in order to minimize unwanted biological "side effects". The diffused molecules are what is measured when plasma concentrations of a neurotransmitter are taken. This plasma concentration is many times smaller then the initial concentration that would be observed at the synaptic terminal at the time of the transmitters release. Therefore, recreating the measured levels of DMT through administration; only small subjective responses are observed as we would expect if DMT is to act as an endogenous neurotransmitter. Both morphine and codeine have been shown to be constituents of the CNS. The concentrations measured are very small being 2–339 fmol/ml [13]. An attempt made to deduce morphine's or codeine's endogenous role in the CNS by recreating these plasma concentrations, would lead to the theory that endogenous morphine and codeine are without biological activity. However, morphine and codeine almost certainly do have a dramatic effect at their synaptic site of release. It is a requirement of the brain to compartmentalize the flow and computation of information while minimizing plasma concentrations of transmitters.

Serotonin response; anxiolytic role reconsidered

The serotonin receptors 5-HT_1 and 5-HT_3 are known to exert anxiolytic effects in mice [14]. As DMT is a known agonist of the 5-HT_1 site [22], it seems likely that the reported anxiolytic effects of low dose DMT administration result from activity of DMT at 5-HT receptors. It is certainly feasible that activity of DMT at a specific subtype of the TA receptor may result in an anxiolytic behavioral response. However, since DMT is known to have activity at 5-HT receptors involved in an anxiolytic response, and the fact that this response is observed at low levels of administered DMT where 5-HT activity is more likely to exert a significant biological response than TAARs, it seems likely that this subjective effect is mediated by 5-HT systems. It seems more probable that the endogenous hallucinogens endogenous role mimics their subjective effects at the higher administered concentrations; that is they act as true endogenous hallucinogens playing a role in sensory perception and experience via a subclass of TA receptors.

The true biological role of the endogenous hallucinogens

Researchers have been puzzled over the role of the endogenous hallucinogens for over 50 years. The endogenous hallucinogens have been hypothesized as playing roles in phenomena such as dreaming [31], near death experiences [32], psychosis [33,34] and more recently even UFO abduction experiences [32]. All of these experiences represent altered states of consciousness (ASC). These ASC are conditional on the existence of a standard waking state. Endogenous hallucinogens may be involved in the above ASC as well as others, however I propose that it is the role these chemicals play in ordinary sensory perception that allows them to precipitate in the ASC as well. Dreaming, psychosis and out of body experiences arise when the release of endogenous hallucinogens is not correlated with external events. In this theory waking reality is created in a similar way to altered states except that the normal state correlates with events in the "physical" world. Thus waking reality can be thought of as a tightly regulated psychedelic experience and altered states arise when this regulation is loosened in some fashion. This model predicts that the sensory altering effects of administered hallucinogens are a result of the hallucinogens acting directly, via the TAARs and the 5-HT receptors, on regions of the CNS involved in sensory perception.

TA vs. 5-HT_{2A}

Many studies have focused on DMT and other indole and phenethylamine hallucinogens as being partial agonists of serotonin receptors, specifically the serotonin 5-HT_{1A}, 5-HT_{2A} and 5-HT_{2C} receptors. While 5-HT activity is certainly responsible for many of the subjective effects of administered hallucinogens, 5-HT activity may not be involved with the action of the endogenous hallucinogens at all, especially if the endogenous hallucinogens act as transmitters. Certain ASC may occur when endogenous DMT comes into contact with 5-HT receptors as well as acting inappropriately on TAAR receptors.

Throughout the past few decades, a significant amount of evidence has enforced the belief that the psychological effects of the hallucinogens result from activity at the serotonin 5-HT_{2A} receptor. It has been shown thoroughly that lysergic acid diethylamide

(LSD), 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI), 1-(2,5-dimethoxy-4-bromophenyl)-2-aminopropane (DOB), 4-hydroxy-*N*,*N*-dimethyltryptamine (psilocin) and 3,4,5-trimethoxyphenethylamine (mescaline) exert many of their behavioral effects through the 5-HT_{2A} receptor in mice [15,16]. The head twitch response (htr) in mice has proven to be an effective, although imperfect, behavioral tool for predicting the hallucinogenic potential of a compound in humans. Hallucinogen induced htr is mediated by 5-HT_{2A} activity as htr can be abolished by pretreatment with 5-HT_{2A} antagonists and htr is absent in 5-HT_{2A} −/− mice [15].

The belief that 5-HT_{2A} activation is responsible for the subjective effects of administered hallucinogens in humans was apparently confirmed in human antagonist studies using psilocybin and the 5-HT_{2A} antagonists' ketanserin and risperidone [17]. Utilizing the Swiss altered states of consciousness (APZ) scale, the 5-HT_{2A} antagonists ketanserin and risperidone were shown to decrease the subjective effects of psilocybin, including the visionary restructialization effects (VR) [17]. Unfortunately these studies were carried out almost 5 years before the discovery of the TAAR family. Therefore, the role of the TAAR family on the subjective effects of administered hallucinogens was unable to be evaluated. Additionally it is unknown if risperidone and ketanserin exert any antagonistic effect on the TAARs. The fact that these antagonists decrease all subjective effects of psilocybin in addition to the existence of several known 5-HT_{2A} agonists whom lack significant visual altering affects (5-MeO-DMT, *N*,*N*-diethyltryptamine (DET), 3,4-methylenedioxyamphetamine (MDMA)) indicate that these antagonists may be exerting an antagonist effect on a subclass of the TAARs in addition to their known activity at the 5-HT_{2A} site. It may be this antagonist activity at the TAARs rather than 5-HT_{2A} that is responsible for the reported decrease in the VR activity of the APZ scale. The selectivity of these antagonists for TAAR sites must be evaluated. More selective antagonists may be needed to effectively resolve this matter. Receptor binding assay projects like McKenna's [22] are indispensable for this type of pairing of subjective effects to receptor activity. Future projects should include hallucinogen affinity for TAAR sites in addition to 5-HT sites, evaluate the antagonist's affinities at all of these sites as well, and evaluate the compounds subjective effects using one of the hallucinogen rating scales.

5-HT_{2A} activation not adequate for Visual activity

5-HT_{2A} activation alone is unable to account for the visual phenomenon common of the classical indoleamine and phenethylamine hallucinogens. This is confirmed by the subjective effects of the 5-HT_{2A} agonists MDMA [10,25], the endogenous tryptamine hallucinogen 5-MeO-DMT [20] and the tryptamine hallucinogen DET [18,19]. These compounds are classified as hallucinogens but are unique in that their subjective effects are reported to be solely emotional [10,20,26] and virtually devoid of the visual phenomenon common of other hallucinogens such as DMT and psilocin.

There are some reports in the literature of DET and 5-MeO-DMT having some visual phenomenon associated with their administration. These individuals may have a specific subtype of the receptor responsible for visual activity which allows greater agonist binding. It may also be possible that these compounds have low affinity for the visual receptor and the visual effects are only observed at high concentrations.

5-MeO-DMT has been shown to have a higher affinity for 5-HT_{2A} than DMT [21,22]. Additionally, it has been shown that relative to DMT, 5-MeO-DMT produces a smaller cAMP response at TAAR1, implying a lower potency at this receptor [3]. Whether this type of activity is common of 5-MeO-DMT at all TAARs is unknown. As 5-MeO-DMT is one of the known endogenous trace amine hallucinogens it seems likely that it acts as a ligand for a specific TAAR not involved in visual perception but rather in some other sensory modality or neural process. It seems likely that the behavioral effects of administered 5-MeO-DMT are mediated strongly by 5-HT_{2A} activity and at least not so much by the TA receptor involved in visual perception although other TAARs certainly may play a role in the reported subjective effects following 5-MeO-DMT administration. Neither DET nor 5-MeO-DMT have been evaluated with the APZ scale or any other hallucinogen rating scale such as the hallucinogen rating scale (HRS). These evaluations will prove valuable in allowing the association of the specific subjective effects of different hallucinogens with each of their unique receptor binding fingerprints. It will then be possible to theoretically assign dose dependent subjective effects to specific receptors. This data will additionally shed light on some of the endogenous roles of the various receptors that hallucinogenic drugs target. As well as lead to novel targets for future highly specific and effective anti-psychotic drugs.

5-HT_{1A} agonism unable to account for lack of visual effect of 5-MeO-DMT

While DMT is one of the strongest visual hallucinogens known it has significantly less affinity (IC_{50} value) for the 5-HT_{2A} receptor than 5-MeO-DMT does, 75 ± 16 nM and 14 ± 1 nM, respectively [22]. Therefore, if 5-HT_{2A} activity is correlated with the visual effects of hallucinogens, 5-MeO-DMT should have strong visual activity. One theory proposed to account for 5-MeO-DMT's lack of visual activity is the theory that agonist activity at 5-HT_{1A} opposes the subjective effects of 5-HT_{2A} activation [12], as 5-MeO-DMT shows greater affinity for 5-HT_{1A} than DMT, 6.5 ± 1.5 nM and 170 ± 35 nM, respectively [22]. 5-HT_{1A} and 5-HT_{2A} activation has been discovered to mediate opposing responses on membrane excitability in the CNS of rats [30]. Strassman showed that pretreatment with the 5-HT_{1A} antagonist pindolol significantly increased the reported psychological response to DMT [12]. One experiment that would clarify if 5-HT_{1A} inhibits the visual activity induced by 5-HT_{2A} activity would be pindolol pretreatment followed by 5-MeO-DMT administration. If the subjects then report the presence of visual activity, the 5-HT_{1A} theory may then be correct, although we must account for the possibility that in addition to dampening the 5-HT_{2A} mediated activity, 5-HT_{1A} may also opposes activity mediated by the TAAR sites. One thing that counters the 5-HT_{1A} theory is that the hallucinogen S (+) alpha-methyltryptamine (AMT) has greater 5-HT_{2A} affinity (46 ± 6 nM) [22] than DMT and significantly less 5-HT_{1A} activity (1900 ± 375 nM) [22] than DMT. While not formally evaluated by any hallucinogen rating scales, racemic AMT has been reported to have minimal visual effects by several subjects [26]. Thus if 5-HT_{1A} and 5-HT_{2A} agonist activity were all that was pertinent for visual activity, AMT would be one of the most potent visual hallucinogens known. Clearly 5-HT activity alone cannot account for the reported subjective effects of hallucinogenic compounds, specifically the visual activity.

Another interesting note is that MDMA has been shown to be an agonist of TAAR1 in mice [3,24] yet it lacks significant VR activity [10]. Certainly not all TA receptors play a role in sensory experience and likewise all TAARs are not the natural receptors of the endogenous hallucinogens, furthermore as the effects of 5-MeO-DMT show us; not all of the endogenous hallucinogens are directly involved in visual perception. TAAR1 may not turn out to be one of the endogenous hallucinogen receptors although it may certainly still prove to play a role in the behavioral effects of administered hallucinogens. Because of its correlation with the positive symptoms of schizophrenia and distribution pattern in the CNS, TAAR6

might represent one of the endogenous hallucinogen receptors. Activation of a receptor expressed in regions of the CNS involved in sensory perception would result in strong VR subjective effects.

Conclusions

Due to the dramatic subjective and behavioral effects of the endogenous hallucinogens it is probable that they act as transmitters rather than hormones of the CNS. As transmitters of the CNS, their activity would be compartmentalized and regulated. When this regulation is faulted psychosis and other ASC would arise. Thus antagonists of the TAARs may represent novel pharmacological targets for treatment of psychotic disorders. While many theories have attempted to associate the endogenous hallucinogens with ASC it is important to recognize that ASC are only possible because of a normal waking state of consciousness. I propose that it is the role which these compounds play in our waking awareness which allows them to play a role in the ASC as well.

A likely candidate for one of the endogenous hallucinogen receptors is TAAR6. TAAR6 is found in several limbic areas as well as the frontal cortex. Additionally mutations in the gene coding for TAAR6 have been implicated in the positive symptoms of schizophrenia. There is much to be revealed about the endogenous hallucinogens. These compounds represent a completely novel area of study which will lead to valuable treatments for psychological disorders as well as to a general advancement of our understanding of the neurochemistry of sensory perception.

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