54.

Psychedelics and Psychosis: Dimethyltryptamine as an Endogenous Psychotogen

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Beginning in the mid-1990s and continuing to the present day, there has been renewed interest and research into psychedelic drugs. One theory that has been given new life is the possibility that the hallucinogen dimethyltryptamine (DMT) is an 'endogenous psychotogen', or a substance produced by the body that causes schizophrenia. As you may know, DMT is present in humans and this theory was initially proposed shortly after DMT-forming enzymes were found to be present in mammalian tissues in 1961. Research into DMT continued in the subsequent decades but ended when it was found that DMT concentrations were generally no higher in schizophrenics than in healthy controls. Here we'll briefly examine this theory in light of new evidence, and demonstrate that a possible role of DMT in schizophrenia still remains viable. This article will be expanded upon in my presentation. Refer to Wong and Van Tol [1] for a good overview of schizophrenia.

Justification for the theory

Sometimes a disease can be understood by knowing how a drug that treats the illness works. This is true of schizophrenia. For example, old-school antipsychotics such as haloperidol are dopamine antagonists; this evidence influenced the 'dopamine hypothesis' – that schizophrenia involves hyperactivity of dopamine pathways in the brain.

Newer, more effective treatments for schizophrenia such as clozapine, known as atypical antipsychotics, are stronger antagonists of serotonin 5-HT_{2A} receptors than dopamine receptors [2]. You may be familiar with this receptor: it's generally thought that hallucinogens such as LSD, psilocybin – and yes, DMT – must act as agonists of serotonin 5-HT_{2A} receptors for their hallucinogenic effects [3]. In other words, DMT acts on the same serotonin receptor subtype implicated in schizophrenia, thereby making the possibility that DMT is involved in schizophrenia biologically plausible.

How can it be shown that DMT is an endogenous psychotogen?

Hollister [4] proposed several criteria for a compound to be an endogenous psychotogen. Here we'll briefly consider the three main conditions as they apply to DMT. The nuances of each point will be considered in greater detail during my talk.

1. The agent must be found in humans

This criterion is met – DMT is produced in humans via a very simple biosynthetic pathway [5]. The essential amino acid L-tryptophan is converted into tryptamine by the enzyme aromatic amino-acid decarboxylase (AADC). Tryptamine then binds to the enzyme indolethylamine-N-methyltransferase (INMT) to form N-methyltryptamine (NMT). Further binding of NMT to INMT produces DMT (dimethyltryptamine).

2. The agent must be capable of mimicking clinical aspects of schizophrenia

In the 1960s, the observation that schizophrenia is a disease exemplified by hallucinations prompted suggestions that hallucinogens such as LSD are pharmacological models of schizophrenia. Others argue that the hallucinogen experience only superficially resembles

schizophrenia [6]. For instance, classic hallucinogens typically produce visual hallucinations, yet auditory hallucinations e.g. hearing voices, predominate in schizophrenia. Clearly then, for DMT to be a psychotogen, we need to demonstrate that aspects of the DMT experience cause disturbances that are somehow similar to those observed in schizophrenia.

In the past few years, several studies have done just this. In these studies, the effects of DMT have been compared against the NMDA antagonist ketamine, the latter being a well-regarded pharmacological model of schizophrenia. For example, after administering both drugs to healthy volunteers, Gouzoulis-Mayfrank et al. [7] reported that DMT may be a more appropriate model of paranoid psychosis than ketamine, and in particular produces prominent thought disorder and inappropriate affect (emotion).

Other studies have focussed on the disturbances in attention that are characteristic of schizophrenia. 'Inhibition of return' reflects an automatic, inhibitory mechanism of attention, which is thought to protect an organism from redundant, distracting sensory information. Deficits in inhibition of return are commonly observed in schizophrenia, an effect which is greater after the administration of DMT than ketamine [8]. DMT also produces disturbances in 'mismatch negativity', a pre-attentive process for detecting changes in a stimulus e.g. sounds, but this deficit is more pronounced after the administration of ketamine [9]. Schizophrenics also display problems in sensorimotor gating, a mechanism that protects us from early stimulus processing and prevents us from experiencing sensory overload. After the administration of DMT and ketamine, however, neither drug was found to produce deficits in sensorimotor gating [10].

3. The agent must be differentially synthesised or metabolised in schizophrenics

It's all well and good to administer DMT to healthy people and show that it can model certain symptoms of schizophrenia. Obviously we must also demonstrate that DMT is present in higher concentrations in schizophrenics, at concentrations high enough to produce these disturbances. This is the major shortcoming of the theory – using sensitive assays, studies have generally been unable to demonstrate that DMT is elevated in schizophrenics in comparison to healthy controls [11].

However, as they say in the classics, the truth is rarely pure and never simple: to date, no study has quantified blood DMT levels in an appropriate manner, and herein lies a possible reason why no differences have been observed.

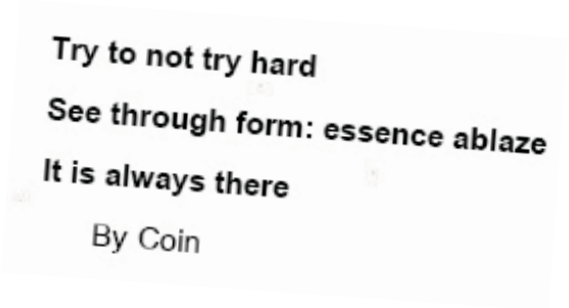
As you may know, DMT is extremely short-acting, and its short duration has lead to it being coined the 'businessman's lunch trip'. Sitaram et al. [12] studied DMT's rapid metabolism by administering DMT in rats. As shown in Table 1, they found that only 1.1% of the administered DMT appeared in the urine unmetabolised as DMT.

Interestingly, however, a substantially greater quantity of the DMT metabolite, DMT-N-oxide (DMT-NO) could be recovered from urine. In fact, by taking into account DMT, and its metabolites DMT-NO and NMT, over 7% of the

administered DMT could be recovered.When pre-treated with a monoamine oxidase inhibitor (MAOI) such as iproniazid, this became over 20%.

Table 1. Mean amount (%) of DMT and its characteristic metabolites recovered from urine during the following 24 hours after administration of 10 mg/kg i.p. DMT in rats. From Sitaram et al. [12].

Pre-treatment	DMT	DMT-NO	NMT	Total
Control	1.1	6.5	.02	7.62
Iproniazid	2.1	20.6	0.6	23.3



What does this all imply? It suggests that previous attempts to quantify DMT concentrations have been flawed, because they've attempted to measure DMT exclusively, when instead they should also be examining the metabolites unique to DMT, specifically DMT-NO and NMT. Instead of measuring ~1% of DMT concentrations, by administering an MAOI such as iproniazid and quantifying its metabolites, a substantially larger concentration of DMT can accounted for.

Therefore, the failure to find any noticeable difference in schizophrenics and controls could be an artefact of inappropriate assays. However, it's entirely possible that regardless of this consideration, the endogenous concentrations of DMT are never sufficiently high for it to act as a psychotogen.

It's also important to note that schizophrenia is a syndrome, or an illness characterised by a cluster of symptoms such as hallucinations and delusions. Because it's a heterogeneous disorder, if DMT is involved in schizophrenia, it's likely that it would only affect a subgroup of people. Therefore, the elevated DMT concentrations in few schizophrenics might be masked by the low levels of DMT in many schizophrenics. The implications of this and the problems it causes for schizophrenia research will be discussed in my presentation.

Other considerations

Jacob and Presti [13] propose that DMT might not be involved in schizophrenia, but instead, mood regulation as an agonist of the newly-discovered TAAR1 receptor [14]. This is supported by the finding that when DMT is administered at low, non-hallucinogenic doses, it has mood elevating properties [15].

It's interesting to note that when given amphetamine, TAAR1 genetic knockout mice display hyperactivity in the mesolimbic dopamine pathway [16, 17]. This is considered an

animal model of schizophrenia because such disturbances are also seen in schizophrenics and are reversed by antipsychotics. Furthermore, tyramine, an endogenous TAAR1 agonist, has been shown to reduce amphetamine-induced hyperactivity of dopamine pathways in mice that do have the TAAR1 receptor [17]. This suggests that TAAR1 agonists may have antipsychotic properties by exerting a modulatory effect on dopamine transmission. As an agonist of TAAR1, this suggests that DMT may paradoxically have antipsychotic properties.

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