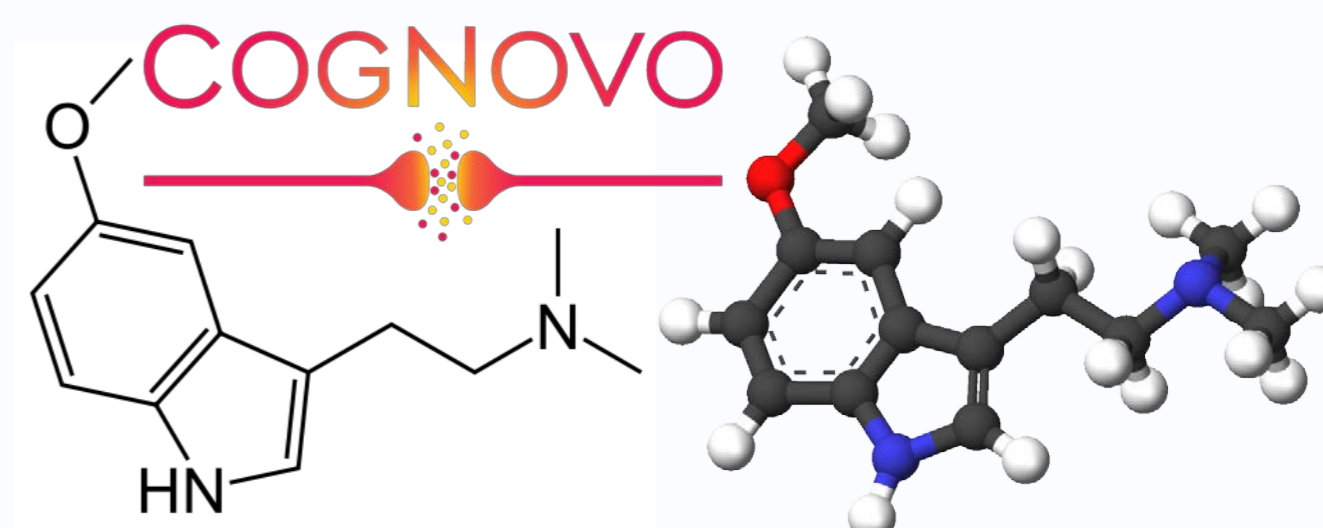


5-Methoxy-N,N-dimethyltryptamine: A novel treatment for addiction



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ABSTRACT: 5-Methoxy-N,N-dimethyltryptamine (acronymized as 5-MeO-DMT) is *sui generis* among the numerous naturally-occurring psychoactive indolealkylamine substances. Research indicates that 5-MeO-DMT may be endogenously synthesized in human pineal and retina. Moreover, it has been detected in blood, urine, and cerebrospinal fluid (Shen et al., 2010). The enigmatic molecule acts as a nonselective partial agonist at the 5-HT_{1A/2A} (5-hydroxytryptamine or serotonin) receptor subtypes (associated with emotions, cognition, and memory, *inter alia*). 5-MeO-DMT is ubiquitously present in the plant kingdom (e.g., in high concentrations in the resin of the *Virola theiodora* tree). Anthropological/ethnopharmacological evidence indicates that various cultures utilised it for medicinal, psychological, and spiritual purposes for millennia. In addition to its phytochemical distribution it is present in the skin and venom of a single amphibian species that is exclusively endemic to the Sonoran desert. Based on recent neuroscientific findings (e.g., Dakic et al., 2017) and numerous anecdotal reports it is postulated that 5-MeO-DMT is a very potent novel treatment for various addictions. Converging evidence from multiple sources is presented to empirically substantiate this hypothesis and to motivate further systematic scientific research.

INCILIUS ALVARIUS: The Sonoran Desert toad (binomial Latin nomenclature: *Incilius alvarius*) produces significant amounts of 5-MeO-DMT in its numerous peripheral parotoid glands (Davis & Weil, 1992). The salience of toad symbolism in Mesoamerican art and mythology is well documented by anthropologist (Furst, 1972). For example, toad-figurines and iconography (with accentuated glands) are found in archaeological excavation from ancient Mayan and Aztec cultures (e.g., "Tlaltecuhltli" [Aztec: tʃaʔte'kwɪtʃi] - the earth or earth mother as a monstrous toad).

QUALITATIVE PHENOMENOLOGICAL EFFECTS: 5-MeO-DMT is extremely neuroactive (4-10 times more potent than its better known close structural relative N,N-Dimethyltryptamine). It has a fast onset (full effects are almost instantaneously present after administration), and a short-lived acute action (ca. 20-50 minutes). Significant anecdotal evidence indicates that 5-MeO-DMT expands and transforms consciousness in profound and linguistically ineffable ways and that it has the potential to induce a temporary non-dualist experiences of reality. In other terms, the dichotomy between subject and object (the observer and the observed) dissipates. This transformational phenomenological experience (cf. McKenna, 1993) has also been described as ego-dissolution or ego-death (Nour et al., 2016) and it is congruent with epiphanies which form the quintessential basis of various ancient contemplative Asian wisdom traditions, e.g., Hinduism and Buddhism (cf. James, 1902). For example, 5-MeO-DMT can occasion experiences that resemble those described by the hinduistic/vedāntic concept of "Advaita" (Sanskrit: अद्वैत वेदान्त) which translates from into English as "not-two" or "no second" – a mystical state of "unity consciousness" which has recently become the focus of modern neuroscience, particularly in the context of meditation (e.g., Josipovic, 2014).



Incilius alvarius



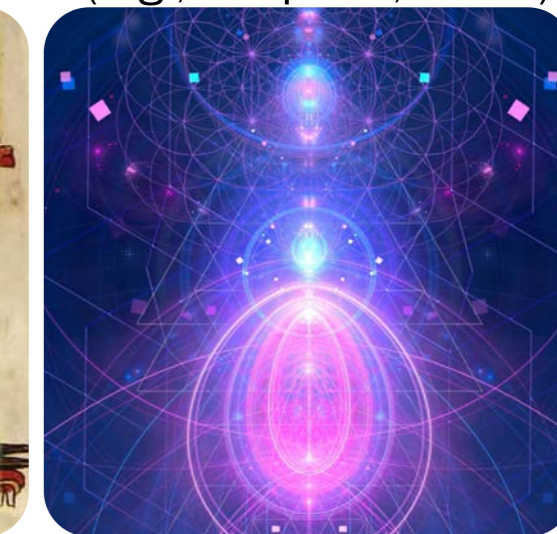
Virola theiodora



Viho snuff from the bark of the Virola theiodora tree



Tlaltecuhltli



Artistic rendering

NEUROCHEMICAL RECEPTOR-BINDING CHARACTERISTICS: 5-MeO-DMT has an exceptionally high affinity for certain members of the 5-HT receptor family. Specifically, this molecule acts as a nonselective partial agonist for the 5-HT_{1A} and 5-HT_{2A} receptor subtypes. The 5-HT system is associated with, i.a., cognition, emotion, and memory. For example, 5-HT receptors are located in the cerebral cortex (cognition), in the amygdala (emotions), and in the raphe nucleus (its projection regulate circadian rhythms, alertness, inhibition of pain, *inter alia*). The raphe nucleus is located in the phylogenetically most primitive part of the brain, the brainstem, and its serotonergic axons project widely throughout the cortex. The raphe nucleus produces the majority of brain serotonin and it contains ≈85% of all the of the serotonin neurons in the brain. Ergo, when it is stimulated by 5-MeO-DMT it causes extensive serotonergic activation throughout many interconnected neural networks of the brain. Moreover, 5-HT receptors are present in the hypothalamus which connects the central nervous system to the endocrine system. It can be cogently argued that 5-MeO-DMT causes the hypothalamus to release large amounts of the neuropeptide oxytocin via the pituitary gland. This increase in oxytocinergic activity might explain why the qualitative linguistic descriptions of 5-MeO-DMTs phenomenology frequently include words like "love", "unity", and "connectedness". Accumulating evidence indicates that 5-MeO-DMT is an endogenous ligand of the Trace amine-associated receptors (TAARs), a class of G protein-coupled receptors that were only recently discovered in 2001. It has been hypothesized that the TAARs are involved in sensory perception. Moreover, TAARs have been associated with pathological neuroadaptations associated with prolonged exposure to addictive drugs (e.g., alcohol, heroin, cocaine, etc.). Consequently, this molecular target might partially explain 5-MeO-DMTs promising neurorestorative and neuroprotective effects in addiction treatment. That is, because 5-MeO-DMT is able to target these receptors it might be able to regulate the pathological neurological adaptations caused by addiction (the neuropsychological "reset-hypothesis"). Furthermore, 5-MeO-DMT has been found to match the σ₁ receptor which regulates cytoskeletal dendritic spine morphology and neurite outgrowth. Therefore, σ₁ receptor agonism may mediate neuroplastic processes which are crucial for positive cognitive/behavioural changes in addiction treatment. In addition, agonism of the σ₁ receptor has been shown to have anti-inflammatory effects. Neuroinflammation likely plays a role in the pathophysiology of various psychopathologies like depression and addiction (e.g., Rodrigues et al., 2014). In addition, a recent cutting-edge *in vivo* and *in silico* study using human cerebral organoids (Dakic et al., 2017) demonstrated that 5-MeO-DMT downregulates the metabotropic glutamate receptor 5 (mGluR5) which has been associated with the pathogenesis of mood disorders and addiction (Terbeck et al., 2015) and is involved in the hedonic rewarding effects of addictive drugs (Knapp & Kornetsky, 2009). The effects of this extraordinary tryptamine on the mesolimbic dopaminergic system (e.g., nucleus accumbens, ventral tegmental area) are currently not well defined and more systematic empirical research is evidently needed to elucidate its exact neuropsychopharmacological mechanisms of action and potential associated epigenetic effects.

5-MEO-DMT AS A PROTOTYPICAL ENTHEOGEN: An entheogen (Ruck et al., 1979) is a chemical substance used in a religious, shamanic, or spiritual contexts that has the potential to produce profound psycho-spiritual changes. The etymology of the neologism "entheogen" is a compound lexeme derived from the ancient Greek ἐνθεος (entheos) and γενεσθαι (genesthai) and translates into "generating the divine within" (cf. "enthusiasm"). 5-MeO-DMT is a prototypical representative of this class of consciousness-expanding substances (Metzner, 2015). For instance, it is a ceremonial sacrament (Eucharist) of the "Church of the Tree of Life" and interdisciplinary research focusing on 5-MeO-DMT (qualitatively and quantitatively) might provide further impetus for the emerging new neuroscientific paradigm which goes by the name "neurotheology". It has been stated by the eminent neurobiologist Efrain C. Azmitia that "the ability of these drugs to induce a feeling of closeness to God is a special property of the indoles and this property is attributed to activation of the cortical 2A serotonin receptor" (Azmitia, 2012).

CONCLUSION: Based on this brief synopsis of pertinent background information I propose the novel hypothesis that 5-MeO-DMT acts as a neuro-psycho-spiritual cathartic catalyst and that it has the potential to become an effective treatment for various addictions (viz., severe substance use disorders according to DSM-5 criteria like alcohol, heroin, and cocaine addiction). The psychopharmacological treatment might be combined with new forms of "transcendental psychotherapy" in order to facilitate the integration of the profound life-changing transformational experience induced by 5-MeO-DMT. Moreover, it is hypothesised that biophilia and deep experiential insights into the fundamental ontological interconnectedness of all of existence play an important role in the psychological healing of addictions. Rigorous investigations of 5-MeO-DMTs neuropharmacological mechanisms of action would broaden our scientific understanding of the common neuropsychological (and psycho-spiritual) basis of various addictions. In the long run this might lead to novel treatment approaches and the development of novel (currently non-existent) pharmacological interventions, for instance, by systematically varying 5-MeO-DMTs molecular structure (cf. Shulgin & Shulgin, 1997) in order to systematically explore structure-activity relationships. The exploration of synergistic effects with other naturally occurring psychoactive substances (e.g., Ibogaine) is another hitherto uncharted and potentially very fruitful research area. Moreover, systematic studies might lead to the discovery of as yet unknown neurotransmitter systems (cf. the discovery of endocannabinoid system). Subthreshold micro-dosing is another promising psychopharmacological intervention which should be scientifically investigated in the context of addiction research. Our current knowledge of 5-MeO-DMT is extremely limited and it is therefore argued that systematic research is needed to further our understanding of this exceptional neurochemical compound. For instance, fundamental methodologically rigorously controlled dose-response studies as those conducted with N,N-DMT (Strassman, 2001) are to date lacking and future studies should fill this knowledge gap to enable a better understanding of 5-MeO-DMTs range of effects. Because 5-MeO-DMT is a natural endogenous building block human neurochemistry science cannot afford to empirically neglect this compound (mainly due to political reasons). As William James aptly formulated in his seminal 'Essays in Radical Empiricism': "To be radical, an empiricist must neither admit into his constructions any element that is not directly experienced, nor exclude from them any element that is directly experienced." (James, 1912/1976, p.42). *Per contra*, innovative scientific research is currently legally highly restricted due to the irrational and non-evidence based (Nutt et al., 2010) generic Class A status of psychoactive tryptamines, cf. the "Psychoactive Substances Act" a *lex specialis* which reached Royal Assent in 2016 and for the first time in human history prohibits all mind-altering substances besides the most harmful ones like alcohol which is explicitly legally exempted. Moreover, the widely distributed stereotypical social stigma against all psychedelics substances needs to be addressed and the disinformation propagandised by the mass-media needs to be countered by sound scientific evidence. For instance, it is a widely held belief that psychedelics are associated with mental pathologies and even suicide. However, rigorous statistical analysis of epidemiological data shows that this belief is false, i.e., psychedelics are not correlated with psychopathologies or suicide (Johansen & Krebs, 2015) whereas legal (and widely advertised) substances like alcohol are clearly neurotoxic (Harper, 2007) (even in moderate doses; e.g., hippocampal atrophy) and have multifarious detrimental societal effects with far reaching ramifications which are easily observable in everyday life. Unfortunately these facts are successfully marginalised by the powerful alcohol lobby which has a large influence on the media landscape and also influences scientific, political, and juridical decisions in order to maximise its shareholder profits (e.g., Casswell, 2016; Hawkins, & Holden, 2014). This irrational situation needs to be forcefully and effectively addressed and an objective evidence based scientific approach is clearly needed. Scientific integrity and non-conformist critical thinking à la Marie Curie are crucial scientific virtues in this context (see also Edwards & Roy, 2017).

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MARIE CURIE ACTIONS

