Review

N,N-dimethyltryptamine and the pineal gland: Separating fact from myth

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Abstract

The pineal gland has a romantic history, from pharaonic Egypt, where it was equated with the eye of Horus, through various religious traditions, where it was considered the seat of the soul, the third eye, etc. Recent incarnations of these notions have suggested that *N,N*-dimethyltryptamine is secreted by the pineal gland at birth, during dreaming, and at near death to produce out of body experiences. Scientific evidence, however, is not consistent with these ideas. The adult pineal gland weighs less than 0.2 g, and its principal function is to produce about 30 µg per day of melatonin, a hormone that regulates circadian rhythm through very high affinity interactions with melatonin receptors. It is clear that very minute concentrations of *N,N*-dimethyltryptamine have been detected in the brain, but they are not sufficient to produce psychoactive effects. Alternative explanations are presented to explain how stress and near death can produce altered states of consciousness without invoking the intermediacy of *N,N*-dimethyltryptamine.

Keywords

N,N-dimethyltryptamine, dimethyltryptamine, pineal gland, indolethylamine N-methyltransferase, sigma-1 receptor, endogenous hallucinogen

Introduction

In the past 20 years there has been a surge of interest in the pineal gland and its postulated ability to produce *N,N*-dimethyltryptamine (DMT). Since DMT is a potent psychedelic when significant dosages are exogenously administered, many people have searched for evidence that it is also produced endogenously in physiologically relevant amounts. This search was largely reinitiated as a result of a documentary and book written by Rick Strassman, titled "*DMT. The spirit molecule*." This present review was prompted by a presentation this author gave at the 2017 Breaking Convention, in Greenwich, UK. After the presentation, several in the audience suggested that I write up my talk for publication.

Historical background

This review will essentially focus on whether or not DMT is produced in the human body. More specifically, is DMT produced in the human body, and especially by the pineal gland in physiologically relevant amounts? It seems clear that DMT can be produced in the body, as well as by the pineal gland, in extremely tiny amounts (Barker et al., 2012, 2013), but the more important issue is whether those amounts are sufficient to affect human physiology.

The pineal gland has a long and mythical history. For example, in pharaonic Egypt, the pineal was equated with the eye of Horus. René Descartes (1596–1650) regarded the pineal gland as the point of contact between the soul, body, and the place where our thoughts are formed. The central location and singularity of the pineal as an unpaired organ, as well as its extensive vascularization, described by Andreas Vesalius (1514–1564), are likely the basis for Descartes' (1596–1650) conceptualization of the pineal as the "seat of the soul," or as the organ coordinating psychophysiological functions. Additionally, the "third eye" of Hindu spiritual enlightenment is described as originally being a third eyeball that atrophied into the pineal gland (cited by Shoja et al., (2016)). As Graham St John notes, "Speculative science on the DMT gland has inspired writers of fiction, screenwriters and musicians who've appropriated the pineal-DMT meme as a device to advance narratives vested in diverse metaphysical perspectives on the human condition." (St John, 2017: 154).

Strassman has proposed that the pineal gland excretes large quantities of DMT during extremely stressful life episodes, notably in the event of birth and death. He conjectured that "pineal tissue in the dying or recently dead may produce DMT for a few hours, and perhaps longer, and could affect our lingering consciousness" (Strassman, 2001). The "blinding light of pineal DMT" enables transit of the life-force from this life to the next (Strassman, 2001: 83).

To begin, one would certainly expect that the loss of the pineal gland, were it to have the great importance suggested by these sources, should have profound implications for mammalian physiology. Yet, pinealectomized rats do not differ from sham-operated rats in total sleep, rapid eye movement (REM) sleep, super-modal high-amplitude non-REM (NREM) sleep (HS2), a measure of NREM electroencephalographic (EEG) delta power, or circadian rhythm amplitude (Mendelson and Bergmann, 2001). Pinealectomy in humans is very rare, but one case report

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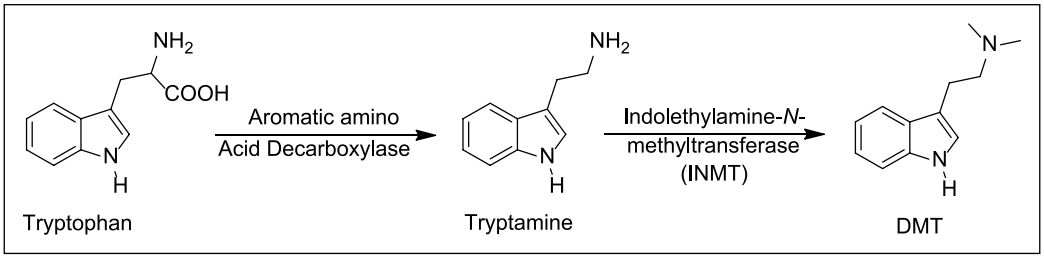

Figure 1. Biosynthesis of *N,N*-dimethyltryptamine (DMT).

indicates that pinealectomy actually increased REM sleep (Kocher et al., 2006). They report no other unusual behaviors after pinealectomy in this patient. In addition, Kunz et al. (1999) have studied pineal calcification and melatonin production. They conclude that the decrease of melatonin production with age is predominantly due to increasing pineal calcification. Yet, they note the lack of association between the degree of pineal calcification and any pathologies.

The pineal gland is a small neuroendocrine organ and its main and most conserved function is the nighttime secretion of melatonin (Sapede and Cau, 2013). Average dimensions of the adult gland are 5–9 mm in length, 1–5 mm in width, and 3–5 mm in thickness; the average adult pineal gland weight has been reported as 100–180 mg, with little apparent variation linked to age or gender (Duvernoy et al., 2000; Macchi and Bruce, 2004). Measured daily secretion of melatonin was lower in women (21.6 μg) than in men (35.7 μg), with constant rates of secretion at night (4.6 μg/h in males, 2.8 μg/h in females) (Fourtillan et al., 2001).

These very small amounts of melatonin are significant, however, because the affinity of melatonin at the human melatonin 2 (MT2) receptor expressed in human embryonic kidney (HEK) cells has been measured as 0.515 nM (Mseeh et al., 2002).

Indolethylamine-N-methyltransferase (INMT)

Proponents of the theory that DMT is produced endogenously in significant amounts point out that the key enzyme necessary for the biosynthesis of DMT, INMT (Figure 1), is present throughout the body, and has high expression in the lungs. INMT was first characterized by Axelrod in 1961 (Axelrod, 1961). The enzyme was identified by incubating [^{14}C]-*S*-adenosylmethionine (SAM) with the soluble supernatant fraction of rabbit lung. He identified radioactive *N*-methylserotonin as the major product. Incubation of N-methylserotonin with radioactive SAM then afforded *N,N*-dimethylserotonin (bufotenine) as the radioactive product. This enzyme was also found to *N*-methylate other phenethylamine derivatives such as phenethylamine, tyramine, mescaline, and dopamine. In a subsequent investigation, Axelrod reported that serotonin (5-HT) was the best substrate for the enzyme, with a K_m of 9×10^{-4} M, but that it also *N*-methylated a variety of other arylethylamines including tryptamine, tyramine, normetanephrine, metanephrine, 3-methoxytyramine, dopamine, and octopamine (Axelrod, 1962). Later, histamine also was found to be a substrate for rabbit lung INMT (Herman et al., 1985).

INMT is widely distributed in mammalian tissues, including the lungs, adrenal gland, thyroid, placenta, heart, pancreas, lymph nodes, retina, pineal gland, and spinal cord ventral horn motoneurons. Since INMT is predominantly present in peripheral tissues, its main physiological function was thought to be non-neural. However, when a dialyzed preparation of rat brain was incubated for two hours at 37°C with 5 mM tryptamine and 30 mM SAM, gas chromatography–mass spectrometry analysis was able to detect very low concentrations of *N*-methyltryptamine, amounting to less than 2 pmol of NMT/mg protein/h (Boarder et al., 1976).

Northern blot analysis of the RNA from 35 human tissues performed with the human INMT cDNA as a probe demonstrated mRNA expression in most tissues, but this was very low or absent in the adult brain (Thompson et al., 1999). Whereas mRNA for INMT was not detected in human brain using northern blot analysis, Cozzi et al. (2011) probed rhesus macaque spinal cord, pineal gland, and retina with rabbit polyclonal antibodies to human INMT protein and reported detectable expression of the enzyme in all three tissues.

Although INMT is present to varying extents in several human tissues, there had not been a definitive determination of whether DMT was actually synthesized in these tissues. Thus, Barker et al. (2013) carried out a qualitative analysis of rat pineal gland microdialysates using liquid chromatography-tandem mass spectrometry (LC/MS/MS). They reported, for the first time, the presence of DMT in pineal gland microdialysate obtained from the rat.

Even though this enzyme was originally discovered as a result of interest in the possible generation of methylated metabolites of tryptamine and 5-HT that might be psychoactive, experimental observations make that possibility less likely. First of all, INMT mRNA is not highly expressed in the brain. Second, the apparent K_m of INMT for tryptamine (270 μM) is relatively high, indicating that although tryptamine served as a useful "prototypic substrate," it is less likely to be an important endogenous substrate for the enzyme. An enzyme with a high K_m has a low affinity for its substrate, and requires a greater concentration of substrate to achieve V_{max} (Thompson and Weinshilboum, 1998). For comparison, the K_m of acetyl choline for acetylcholinesterase is reported as 14.8 μM (Wallace and Gillon, 1982), of dopamine at membrane bound catechol-*O*-methyltransferase is 15 μM (Mannisto and Kaakkola, 1999), and of histamine for rabbit lung histamine *N*-methyltransferase is 11.0 μM (Herman et al., 1985).

Furthermore, DMT is a known inhibitor of INMT, with an IC50 of 67 μM (Chu et al., 2014; Thompson and Weinshilboum, 1998), indicating that any high local concentration of DMT that was formed would actually inhibit the enzymatic production of more DMT.

How much DMT would be required for psychoactive effects?

The best data come from the 1994 study by Strassman and Qualls (1994). A subsequent analysis of plasma DMT levels from the Strassman experiment by Gallimore and Strassman (2016) indicated that breakthrough into the "DMT space" occurs when the effect site concentration reaches ~60 ng/mL, which is 318 nM of DMT base; the K_i of DMT at the human 5-HT_{2A} receptor is reported as 65 nM (Blair et al., 1999). Gallimore and Strassman (2016: 6) state:

> We developed an infusion protocol that maintains an effect site concentration of 100 ng/mL in a 75 kg subject. An initial bolus of 25 mg infused over 30 s rapidly brings the effect site concentration to just over 100 ng/mL. Although the plasma concentration spikes at over 200 ng/mL, the desired effect site concentration is reached smoothly with very little overshoot. The infusion begins at 2 min at a rate of 4.2 mg/min.

These data give an indication of the approximate plasma levels of DMT that would have to be achieved in order to produce the extraordinary psychoactive effects of DMT. That is, if the pineal gland were producing DMT for an out of body experience, it would need very rapidly (over perhaps no more than a minute or two) to produce about 25 mg of DMT. Keep in mind that the mean daily output of melatonin from the pineal gland is approximately 30 μg, about 1/1000 of the weight of DMT needed to activate the "DMT space." How would this gland suddenly gain the capacity to produce such a prodigious amount of a substance that is ordinarily detected there only in very trace amounts?

Human serum does contain sufficient L-tryptophan precursor to produce a relevant amount of DMT, with Comai et al. (2010) reporting a human serum concentration of 12.98 μg/mL (63.56 μM). The question to be asked is where would the biochemical material come from to convert a significant portion of it into DMT?

Can DMT be concentrated in the brain?

The rational scientist will recognize that it is simply impossible for the pineal gland to accomplish such a heroic biochemical feat. To offer a partial explanation, some have suggested that perhaps DMT can be concentrated or accumulated in the brain. In an early review by Barker et al. (1981: 106), one finds the statement, "There is also evidence that DMT is taken up into synaptosomes and stored in vesicles by mechanisms identical to those described for known neurotransmitter substances". There is no citation provided to support that contention, and no study has been reported to date to support that conclusion.

Some reports have suggested that DMT may be actively taken up by the brain. For example, Cohen and Vogel (1972: 1214) report measuring a brain/plasma ratio for DMT of 5.4 after intraperitoneal (IP) injection of DMT in rats, and suggest that this brain/plasma ratio seems "to indicate that the compounds cross the blood-brain barrier easily and are perhaps accumulated by an active transport". Despite that speculation, they also report that DMT "had disappeared from the brain, liver and plasma within 30 min."

A similar brain/plasma ratio of [^{11}C]DMT after intravenous (IV) injection into rats was reported by Takahashi et al. (1985). These workers note that [^{11}C]DMT was relatively highly accumulated in the brain, and its accumulation was retained. Their evidence for accumulation was apparently a very slight increase in brain concentration in the first 10 min after drug was administered, after which the brain concentration slowly declined over the next 50 min. Importantly, they did not pretreat their animals with a monoamine oxidase (MAO) inhibitor, and did not actually analyze tissue for unmetabolized DMT, but only measured radioactivity. Thus, given the known rapid in vivo deamination of DMT, it must be questioned whether what was actually measured in their experiments was intact DMT.

Yanai et al. (1986: 144) examined the subcellular distribution of [^{11}C]DMT in male Wistar rats. Rats were pretreated six hours before experiments with 5 mg/kg IP reserpine, and with 75 mg/kg of IP pargyline two hours before experiments. [^{11}C]DMT was transported readily through the blood-brain barrier and they suggest that the DMT accumulation had the properties of an active uptake mechanism in the experiments using rat brain cortical slices. Without experiments to test this conclusion, it must remain speculative. Importantly, reserpine, which inhibits re-uptake of neurotransmitters into the synaptic vesicles, had a negligible effect on the subcellular distribution, and the authors state that it "was not expected that [^{11}C]DMT would accumulate in the synaptic vesicles of nerve endings in vivo".

It is worth pointing out that the brain/plasma ratio is not a specific proof of active transport into the brain. For example, the antipsychotic agent aripiprazole is not actively taken up into the brain, yet also has a brain/plasma ratio of about five (Shimokawa et al., 2005).

To provide some perspective, it is known that the antihistamine diphenhydramine (DPHM; Benadryl) is actively taken up into the brain (Mahar Doan et al., 2004). These investigators reported a brain-to-plasma ratio of 18.4, and a brain-to-unbound plasma ratio of 115, confirming a high distribution of DPHM to and within the brain. Active transport was later validated by an in vitro assay using TR-BBB13 cells (Sadiq et al., 2011).

A report by Vitale et al. (2011) has also been cited as support for the active transport of DMT into the brain. That study, unfortunately, is fatally flawed because all of their conclusions are based on their use of [^{131}I]-2-iodo-DMT rather than DMT itself. The addition of the iodine atom at the 2 position of DMT will likely convert it into an antagonist at the 5-HT_{2A} receptor, thus abolishing its psychoactive properties (Cerletti and Rothlin, 1955). In addition, iodine is a lipophilic atom and will increase the cLog P of DMT from 1.8 to 2.51 for the 2-iodo analogue. The authors also note that they failed to identify any metabolites, suggesting that 2-iodo-DMT is not a substrate for monoamine oxidase. The authors indicate that up to 0.1% of the injected dose was still detected in the olfactory bulb seven days after injection and conclude that they have demonstrated that exogenous DMT can remain in the brain for at least seven days after injection. Unfortunately, in no respect can their conclusions regarding 2-iodo-DMT apply to DMT itself.

The fact that only trace amounts of DMT have been detected in any mammalian tissue has led to the question of whether any process exists whereby endogenous DMT could somehow be concentrated to reach sufficiently high in vivo levels. In an attempt to address that possibility, Cozzi et al. (2009) proposed

that DMT could reach high local concentrations within neurons through a process involving uptake across the plasma membrane, followed by accumulation into synaptic vesicles. They reported that DMT inhibited [^{3}H]5-HT transport with a K_i of 4 μM at the serotonin reuptake transporter (SERT) in human platelets. The K_i for inhibition of [^{3}H]paroxetine binding to the platelet SERT was >47 μM. They cite earlier studies by others indicating that substrate compounds are more potent at inhibiting 5-HT transport than they are as competitive inhibitors of SERT uptake blocker binding. High ratios are indicative that the compounds are substrates of the SERT, and hence they infer that DMT is a substrate at the SERT, with a ratio of uptake to binding inhibition of >47:4, ≥11. They use similar data and reasoning to conclude that DMT is also a substrate for the human vesicular monoamine transporter (vMAT).

As a technical point, the vMAT used in that study was expressed in insect SF9 cells. It is not clear that vMAT expressed in these cells will recapitulate the exact functional properties of the mammalian vMAT within neuronal endings. Even it if does, however, this does not imply that DMT is necessarily accumulated within neuron vesicles. There are many compounds that are substrates for the SERT and vMAT for which there is no evidence that they are accumulated in neuronal endings.

First of all, recall the earlier discussion here of the work by Yanai et al. (1986) where reserpine had a negligible effect on the subcellular distribution of [^{11}C]DMT. Because reserpine is an inhibitor of the vMAT, the authors therefore state that it "was not expected that DMT would accumulate in the synaptic vesicles of nerve endings in vivo."

A reversal of the transport direction of SERT (Cinquanta et al., 1997; Crespi et al., 1997; Wall et al., 1995) constitutes the action of SERT substrates such as methylenedioxymethamphetamine (MDMA). The reversal of SERT operation to extrude 5-HT from the neuron following uptake of a SERT substrate has also been termed calcium-independent, carrier-mediated efflux or release (Hilber et al., 2005). Models have been developed to explain the releasing action as a consequence of the translocation of the releasing agent by the plasmalemmal transporter into the cell, followed by a conformational change of the protein, facilitating outward transport of the monoamine (Attwell et al., 1993; Levi and Raiteri, 1993).

The SERT (and the other monoamine carriers) can be induced to operate in the reverse direction by SERT substrates, including 5-HT and tyramine, as well as amphetamine derivatives such as para-chloroamphetamine (pCA) and MDMA. These substrate compounds lead to a concentration-dependent increase of [^{3}H]5-HT efflux rate from the neuron terminal. Calculated EC50 values for [^{3}H]5-HT efflux in response to pCA or MDMA were 6.73 μM and 2.87 μM, respectively. An effective oral dose of 125 mg of MDMA hydrochloride in humans is reported to lead to a plasma level of 236 μg/L, or 1.22 μM (de la Torre et al., 2000). Based on data for MDMA-stimulated [^{3}H]5-HT efflux from human SERT stably expressed in HEK cells, MDMA concentrations >1.0 μM are effective at releasing [^{3}H]5-HT in vitro (Hilber et al., 2005).

Although Cozzi et al. (2009) did not determine whether DMT could release neuronal 5-HT, experiments by Berge et al. (1983) with the structurally-related 5-MeODMT found that it inhibited the uptake of [^{14}C]5-HT in rat striatal (IC50 2.8 μM) as well as in hypothalamic (IC50 2.2 μM) synaptosomal preparations. For both structures, inhibition was observed for 5-MeODMT concentrations of 0.5 μM and higher. Concentrations of 5-MeODMT above 10 μM significantly increased the release of [^{14}C]5-HT from preloaded rat striatal synaptosomes. These IC50 concentrations are similar to the K_i of 4 μM for DMT inhibition of [^{3}H]5-HT uptake found by Cozzi et al. (2009).

More recently, Blough et al. (2014) studied the ability of a large series of tryptamines to act either as reuptake inhibitors or as substrates at the dopamine transporter (DAT), norepinephrine transporter (NET), and SERT. They found that DMT was a SERT-selective releaser, with an EC50 value of 114 nM.

The important point to be made here is that even if DMT is a substrate for the SERT or the vMAT, the more likely outcome is that DMT will induce the release of neuronal 5-HT, in a mechanism similar to that of amphetamines such as MDMA. There is no evidence to suggest that amphetamines are actually stored in neuronal vesicles, or that they are released in relevant concentrations in a calcium-dependent manner when the neuron generates an action potential. The same arguments would apply to DMT; being a substrate for the SERT is not evidence that it would accumulate within the neuron and be released in physiologically relevant concentrations.

One key experiment that would resolve this issue definitively would involve incubation of radioactively-labeled DMT with synaptosomes from rats that had been treated with a MAO inhibitor. Any potential accumulation could thus be studied directly in a clear-cut way. In addition, use of reserpine to block vesicular uptake of radiolabeled DMT also would address the question of storage in neuron vesicles.

DMT and the sigma-1 receptor (S1R)

It also has been suggested that DMT is an endogenous ligand for the S1R, although that finding would have doubtful relevance for a central nervous system (CNS) effect. The K_D for DMT at the S1R was reported as 14.75 μM (Fontanilla et al., 2009). Yet, the work by Strassman and Qualls (1994) shows a peak plasma concentration of 90 ng/mL after an IV dose of 0.4 mg/kg, corresponding to a plasma concentration of 0.478 μM. Thus, the K_D of DMT at the S1R is approximately 30-fold higher than the highest concentrations obtained by intravenous administration in the Strassman and Qualls (1994) study. No effective mechanism has been proposed that would allow concentrations of endogenous DMT to accumulate that would be high enough to activate the S1R, and such proposals by Frecska et al. (2013) are addressed by this review.

Low levels of the S1R are found in all CNS regions, but are most abundant in the motoneurons (MNs) of the brainstem and the spinal cord. Mavlyutov et al. (2012) reported that INMT is also localized to postsynaptic sites of C-terminals in close proximity to the S1R. This close association of INMT and S1Rs may suggest that DMT could be synthesized locally to activate S1Rs in MNs. That speculation remains unproven, however.

Fontanilla et al. (2009) indicate that DMT injection induces hypermotility in rodents concurrently treated with the MAO inhibitor pargyline (citing Jenner et al. (1980: 935), and state that "this action is not antagonized by blockers of dopamine or 5-HT receptors," implying that this hypermotility may be due to S1R activation. In fact, Jenner et al. (1980: 69) state that "The hyperactivity component of the DMT-induced behavioral syndrome in pargyline-pretreated mice was… inhibited by cinanserin, haloperidol, pimozide,

methiothepin and propranolol". Further, injection of an amount of exogenous DMT that is massive relative to amounts likely to be produced in vivo seems an irrelevant experiment when discussing a role for endogenous DMT.

If not DMT, then what?

One explanation for out of body experiences, e.g. at near death, could be the production of dynorphin (DYN) and other endogenous opioid peptides. Accumulating evidence suggests that DYN and its cognate kappa-opioid receptor (KOR) play an important role in regulating stress responsiveness, motivation, and emotion (Bruchas et al., 2010; Donahue et al., 2015; Knoll and Carlezon, 2010; Van't Veer and Carlezon, 2013).

DYN peptides fulfill the criteria for neurotransmitters (Chavkin, 2013). DYN 1-13 is an extremely potent agonist, with 0.44 nM affinity at the kappa receptor in rhesus monkey brain (Emmerson et al., 1994). Readers will appreciate that salvinorin A, the hallucinogenic component of *Salvia divinorum*, is a selective and potent agonist at the KOR that can produce hallucinogenic and out of body experiences (Roth et al., 2002). Other endogenous opioid peptides are produced during stress and would activate other classes of opioid receptors.

Jimo Borjigin's laboratory has published some rather remarkable results relevant to cardiac arrest. They have reported that cardiac arrest in rats stimulates a marked surge of global coherence of EEG signals. In addition to an increase of gamma power, a large increase of mean coherence for gamma oscillations was detected at near-death. That is, mammalian brain activity becomes transiently and highly synchronized at near-death (Borjigin et al., 2013).

Their data suggest that the mammalian brain has the potential for high levels of internal information processing during clinical death. The levels of connectivity for all rats at near-death were nearly as high as waking for all frequency bands (except for delta) and significantly higher than under anesthesia. The return of these neural correlates of conscious brain activity after cardiac arrest at levels exceeding the waking state provides strong evidence for the potential of heightened cognitive processing at near-death. They point out that the evidence of highly organized brain activity and neurophysiologic features consistent with conscious processing at near-death provides a scientific framework to begin to explain the highly lucid mental experiences reported by near-death survivors.

In another publication from the same laboratory, Li et al. (2015) emphasize that asphyxia generates a "brainstorm." An immediate and sustained surge of a large set of core neurotransmitters within the cortex occurs in response to asphyxia. In both frontal and occipital cortices, a dramatic and significant surge of neurotransmitter secretion was detected for as long as 20 min of asphyxia for all neurotransmitters tested. These include:

1. Cortical norepinephrine exhibited more than 30-fold elevation within the first minute of asphyxia. In addition to its central effect on arousal and alertness, it also activates adrenergic receptors that are co-expressed on apical dendrites of cortical pyramidal cells, the same anatomic location where 5-HT_{2A} receptors are expressed (Santana et al., 2013).
2. 5-HT surged more than 20-fold within the first two minutes of asphyxia. Activation of 5-HT_{2A} receptors is the mechanism whereby hallucinogenic drugs induce visual hallucinations and mystical experiences in humans.
3. Cortical dopamine surged more than 12-fold within the first minute of asphyxia, and plays important roles in arousal, attention, cognition, and affective emotion.
4. In addition, hypoxic/ischemic injury in adult brain induces excessive release of the excitatory amino acid, glutamate (Hilton et al., 2006). Increased brain glutamate concentrations also can lead to out of body and hallucinogenic experiences (Browne and Lucki, 2013; Gouzoulis-Mayfrank et al., 2005).

Conclusion

Based on the studies reviewed above, a number of conclusions seem to merit consideration.

1. DMT is not produced in concentrations significant to activate CNS 5-HT_{2A} receptors, and is rapidly broken down by MAO if it is produced.
2. There is no evidence to suggest that DMT can accumulate within the brain or within neurons at physiologically relevant concentrations; such inferences are either not supported by direct experimental evidence or are based on flawed experiments.
3. Endorphins, especially DYN, are released during stress, and DYN has very high affinity for the KOR, which can mediate hallucinations and out of body experiences. Other endorphins can mediate euphoria and analgesia through activation of mu or delta opioid receptors.
4. Asphyxiation or cardiac arrest paradoxically lead to brain activation and result in marked increases of brain neurotransmitters such as dopamine, norepinephrine, and 5-HT, the latter of which can stimulate 5-HT_{2A} receptors.
5. Asphyxia induces excessive release of the excitatory amino acid, glutamate. Drugs such as ketamine, which also raise cortical glutamate, can produce out of body experiences.
6. Although the romantic notion that DMT is released from the pineal gland to produce altered states of consciousness at various times of stress is appealing to some, more well-studied systems provide more sound explanations for out of body experiences.

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