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Psychedelic medicine: The biology underlying the persisting psychedelic effects

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ABSTRACT

Psychedelic substances have regained interest as therapeutic agents in the treatment of stress-related disorders. The effects seem to be of persisting nature even after a single dose. Also in lower than 'regular' recreational doses, so-called micro-doses, without the typical effects on consciousness, users report beneficial effects on cognitive processes and well-being. The exact neurobiological mechanism underlying these persisting effects is not clear. While previous research has mainly focused on the central nervous system including the immune system and the neuroendocrine system, I propose a central role for sleep and the microbiome in the effects of regular and low doses of psychedelics respectively. It will be explained why this is hypothesized and studies to test this idea proposed. It is concluded that while these studies are needed to understand the biology underlying psychedelic medicine, it is also important to approach it in a holistic way, including all the above mentioned biological processes psychedelics are known to affect, and explore the role of other substance-related factors like route of administration and form, and factors like diet and lifestyle which are part of the psychedelic experience.

Introduction

Psychedelics like psilocybin, ayahuasca, and LSD have regained interest as therapeutic tools in the combatting of severe, debilitating, stress-related psychopathologies like anxiety disorders and depression [9,45]. Recently two experimental studies provided evidence for their therapeutic potential in treatment-resistant depression, with acute symptom improvement persisting up to seven days after a single dose of ayahuasca [48] and up to six months after two sessions with psilocybin [7].

While caution is warranted seen the preliminary state of these findings [5], it is nonetheless interesting and remarkable that these substances work for patients who are unresponsive to other treatments [7,48]. In a survey study psychedelics were reported to be more effective than conventional treatments by psychedelic users who self-medicated to combat their psychopathologies [39] and non-pathological users were shown to display a decrease in self-rated stress and depressive affect which lasted up to four weeks after a psychedelic session in a naturalistic setting [66].

While research into the acute and longer-term effect of *regular* 'recreational' doses of psychedelics on behavioral and emotional state is gaining track, another phenomenon, *micro-* or *low*-dosing with psychedelics is receiving increased attention by users, media and now also scientists [25,70]. Micro-dosing refers to the practice of taking 1/10th of a regular dose repeatedly according to some kind of scheme, e.g., taking doses and leaving two dose-less days in between [18]. Anecdotal evidence suggests that this practice is effective in combatting symptoms of ADHD or just improving concentration or enhancing creativity [18]. Even though psychedelics, in low or regular doses, seem to have therapeutic potential in combatting psychopathologies and enhancing mood, well-being, and cognitive processes, in 'healthy' individuals, the biology underlying these persisting or longer-lasting effects beyond the acute state, when the drug has left the system is not clear.

It is suggested that psychedelics are serotonergic agents exerting their *acute* effects on mood and behavior via the serotonin (5-hydroxytryptamine; 5-HT) 2A receptor where they act as an agonist [34,67]. Current research has mainly focused on role of the central nervous system (CNS) [30] including the immune system (inflammation) [62], the neuroendocrine system [57], large brain networks (e.g. default mode network, executive control network) (e.g. [8,29]), and neuroplasticity within these networks [11,36], and the circadian rhythm (sleep) [4,44] as biological substrates of the full psychedelic experience, i.e., after a regular dose of psychedelics.

While there is some evidence that psychedelics affect these biological processes acutely the full biological mechanism underlying the (persisting) psychological effects is not clear. Below I propose two biological processes which I think underlie these persisting effects after a regular and a low dose of psychedelics. I suggest that a regular dose

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targets directly the central level, more specifically sleep and that a low dose indirectly targets central level processes via the gut. I acknowledge that all the mentioned biological systems work in an interactive way to produce the persisting effects though this will not be discussed as this is beyond the scope of this paper.

Regular doses of psychedelics and sleep

Sleep disturbances are highly prevalent in depressive patients with more than 80% of them having complaints of poor quality sleep [46,49]. The sleep symptoms are often unresolved by first-line treatment and are associated with a greater risk of relapse and recurrence [46]. Interestingly, sleep problems often appear before other depression symptoms, and subjective sleep quality worsens before the onset of an episode in recurrent depression [46]. Brain areas showing increased functional connectivity with poor sleep scores and higher depressive symptomatology scores included prefrontal and limbic areas [12], areas involved in the processing of emotions. Disruption of sleep in healthy participants has demonstrated that sleep is indeed involved in mood, emotion evaluation processes and brain reactivity to emotional stimuli. An increase in negative mood and a mood-independent mislabeling of neutral stimuli as negative was for example shown by one study [14] while another demonstrated an amplified reactivity in limbic brain regions in response to both negative and positive stimuli [23].

Previously it was shown – by two studies assessing brain activity (EEG) during sleep – that psychedelics (ayahuasca and LSD) affect sleep patterns, inhibiting [4] or lengthening [44] rapid eye movement (REM) sleep or enhancing non-REM sleep stages [4]. Of note, psychedelics exert agonistic action at the serotonin (5-HT) 2A receptor [50,65]; a receptor with suggested over-density in depression [16] and also a receptor known to play a role in sleep [31].

While we have our circadian clock, located in our brain, regulating our sleep/wake cycle, we also have individual *clock genes* that regulate the activity of this clock [40,41]. Preclinical work has demonstrated downregulation of 'clock genes' after a dose of ketamine, suggesting the potential involvement of the circadian clock in rapid antidepressant responses [6]. In line with this, it has been shown that partial or a full night of sleep deprivation can alleviate symptoms of depression suggestible by resetting circadian rhythms via modification of clock gene expression [1,35].

I suggest that a single dose of a psychedelic causes a reset of the biological clock underlying sleep/wake cycles and thereby enhances cognitive-emotional processes in depressed people but also improving feelings of well-being and enhancing mood in *healthy* individuals. This hypothesis can be tested in experimental placebo-controlled studies in (healthy) humans where sleep is for example manipulated (e.g. sleep restriction) after which a psychedelic is given and the effects on sleep (EEG), cognitive processes and mood are assessed. Seen the involvement of the 5-HT2A receptors in sleep, mood, cognitive processes, and the psychedelic experience, *mechanistic* placebo-controlled experimental studies can be conducted combining psychedelics with the 5-HT2A/C receptor antagonist ketanserin and assessing the effects on sleep (EEG), mood and cognition and compare it with the state and performance after a psychedelic alone and after placebo to test the role of this receptor in the effects of the psychedelic on sleep and behavioral processes.

Micro-doses of psychedelics and the gut

As previously stated, converging evidence from preclinical studies suggests that classical psychedelics produce their effects primarily through agonistic actions at cortical 5-HT2A receptors [67]. It has been shown that the therapeutic effect of psychedelics is related to the intensity of the psychedelic experience [55]. Per definition low doses of psychedelics (micro-doses) are *sub-perceptual* and therefore do not induce a psychedelic experience [18]. Nonetheless individuals attribute positive effects to low doses while from a pharmacological point of view it is difficult to understand that a low dose could even have effects on the central *brain* level [38]. I propose that low doses of psychedelics exert their effects via an *indirect* 'central' route, i.e., via the gut.

In recent years the interest in the bi-directional communication between the gut and the brain has risen exponentially [13]. This axis includes the enteric nervous system, consisting of neurons embedded in the lining of the gastrointestinal (GI) tract, the parasympathetic and sympathetic branches of the autonomous nervous system, and the neuroendocrine and neuro-immune system [21]. A key concept is the gut *microbiome*, a collection of micro-organisms in the gut, regarded as a critical node in the brain-gut axis. It has been demonstrated that microbiota can influence CNS function and vice versa via effects on the gastrointestinal tract [13,47,61]. Scientific evidence of this gut-brain axis interaction was for example provided by an animal study in which gut microbiota-free rats, transplanted with microbiota from depressed patients, developed depression-like features [33].

More research starts to show that diet, consisting of macronutrients (e.g. carbohydrates), micronutrients (e.g. vitamins), and *phytochemicals* (non-nutrient bioactive compounds) can directly impact the composition and metabolic activity of the *gut microbiota* and consequently affect both physical and mental health and it is linked with emotional well-being and psychopathologies [3,13,22,52,58,61]. In addition, evidence to support the therapeutic effects of microbiota and probiotics on the symptoms of stress-related psychopathologies is growing [56].

The bacteria in the gut can be divided into two large classes or *phyla*, the Firmicutes, and Bacteroidetes, and two smaller phyla, Proteobacteria and Actinobacteria, together accounting for 98% of all the gut bacteria. Each of these classes contains *pathogenic bacteria* like Clostridia and Campylobacter and *psychobiotics* like Lactobacillus and Bifidobacteria [2,37]. Interestingly, tryptophan supplementation (diet) in piglets led to a change in the microbiome with an increase in two bacteria (Prevotella and Roseburia) known to regulate intestinal homeostasis in humans and animals, and a decrease in two other bacteria (Clostridium sensu stricto and Clostridium XI) also known as pathogens [32]. Another study in humans showed that bacteria in the GI tract of patients were influenced by their medication even reflecting the combinations of medications that were taken [54]. Of note, psilocybin and ayahuasca are two phytochemicals [43] ending up in the gut after oral administration [68].

Interestingly, serotonergic drugs have previously been shown to affect GI tract, next to the CNS, with selective serotonin reuptake inhibitors, for example, being of therapeutic value in the treatment of GI disorders [22] and ayahuasca inducing GI problems like nausea, vomiting, and diarrhea [28]. An explanation for this is that serotonin is a key signaling molecule in both the gut and the brain. Approximately 95% of the 5-HT is located in the GI tract and the remaining 5% is found in the brain [27,47,53]. Next to serotonin, its receptors are also present in both brain and gut, though with different functions in respective locations [22,42,71]. The 5-HT_{2A} receptor, for example, the main target of psychedelics, is peripherally implicated in the contraction of gut smooth muscle [20,47] and centrally in higher-order cognitive processes and mood [42,71].

A potential route of communication between the gut and the brain is via the so-called *kynurenine pathway* [15,26]. This pathway, which is the primary route for tryptophan metabolism, plays a critical role in numerous CNS and GI processes, and stress is known to activate it, inducing the metabolism of tryptophan [26,47]. Since psychedelics are known to cause an elevation in cortisol levels [24,60] they can be regarded as 'biological' stressors, suggestible promoting the metabolism of tryptophan. Tryptophan, the precursor of serotonin, is metabolized into kynurenine, and next into kynurenic acid and quinolinic acid. In general, the latter doesn't cross the blood-brain barrier while the former does, where it acts as an NMDA antagonist and it is known as a neuroprotective compound [47,59].

I suggest that low doses of psychedelics induce their effects via alterations in the microbiome and related pathways to the brain. Again, placebo-controlled experimental studies both in animals and humans are suggested to study this. Preclinical studies are suited to test whether psychedelics affect the microbiome and also test whether this is the case for psychedelics with a different origin, e.g. natural, plant products and synthetic, chemical analogues, that both produce the same mind-altering effects. Since metabolomes, biomarkers of the microbiome activity, like tryptophan and kynurenine, are sensitive to detect differences between people when studying the influence of a diet on health [52] it is suggested to include these when testing the effects of psychedelics on the microbiome. In addition, clinical studies can add a psychological component and test whether potential changes in the microbiome are related to changes in mood and higher-order cognitive-emotional processes.

Discussion

A central role of sleep and the microbiome were suggested – in the present paper – in the persisting psychological effects of psychedelics in respectively regular and low doses; placebo-controlled experimental studies were proposed to test the roles of these two biological processes in the psychedelic effects. Additional studies including both low and regular doses of psychedelics or combining the data of low- and regular-dose studies are needed to be able to directly compare the effects of the different doses on both sleep and the microbiome, and other biological systems (immune system, the neuroendocrine system, large brain networks and the neuroplasticity in those networks). While these hypotheses are testable as suggested, some additional factors also need some consideration.

The gut and diet

The gut microbiome plays a key role in the absorption and digestion of ingested food but consequently can rapidly be altered following dietary alterations [47,52]. Of note, people attending psychedelic sessions are often 'prescribed' a very strict diet beginning before the experience and lasting – in some cases – several weeks, to months, to even years after the experience [69]. It can be suggested that this change in diet could contribute to the positive effect of psychedelics on mood and well-being, experienced after use of the psychedelic, either in the lab or in a naturalistic setting. Moreover, while a dietary intervention involves modifying many lifestyle parameters it is also known that other factors influence the microbiome in a more pronounced way, like general lifestyle [52]. Of note here, one of the motivations to use psychedelics is to cause a change in lifestyle [64] which in itself could lead to alteration of the microbiome.

Different psychedelics, forms, and route of administration

As previously mentioned psychedelics can be of natural but also synthetic origin. It would be of interest to test whether the same compound e.g. psilocybin, administered as natural ('magic' mushroom or truffles) or as synthetic substance produces similar bio(psycho)logical effects since the former might contain additional nutritional components compared to the latter one, affecting the microbiome differently [51] resulting in other behavioral or psychological effects. Additionally, the route of administration and the 'form' might affect the experience. Anecdotal reports suggest, for example, that ingestion of Psilocybe or Amanita muscaria mushrooms via a tea or by just eating defines the experience with the former producing less physical discomfort and a smooth transition into an altered state of consciousness compared with the latter [17,19]. While the oral route of administration is the most common for psilocybin scientific research has also administered it intravenously (IV) [10]. Psilocybin needs to be converted into the psychoactive psilocin and when taken orally this transformation takes place during first-pass liver metabolism; when administered IV, it is changed into psilocin in the kidneys [63]. This other biological route might affect the resulting experience, a hypothesis which has to be tested.

Conclusion

It is said that the modification of both sleep and the microbiome might be additional, alternative therapeutic routes in treating serotonergic-linked disorders [1,35,47] and psychedelic drugs might fit this description. To understand the neurobiological underpinnings of psychedelics' persisting effects on mental well-being we must zoom out and include the additional biological process of sleep and the gut-brain axis in our psychedelic research and explore the role of other substance-related factors like route of administration and form, and factors like diet and lifestyle which are part of the psychedelic experience.

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Conflict of interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.mehy.2019.02.029.

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