Perspective

Effects of serotonergic psychedelics on mitochondria: Transdiagnostic implications for mitochondria-related pathologies

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Abstract

The use of serotonergic psychedelics has gained increasing attention in research, clinical practice and society. Growing evidence suggests fast-acting, transdiagnostic health benefits of these 5-hydroxytryptamine 2A receptor agonists. Here, we provide a brief overview of their benefits for psychological, cardiovascular, metabolic, neurodegenerative, and immunological pathologies. We then review their effect on mitochondria including mitochondrial biogenesis, functioning and transport. Mitochondrial dysregulation is a transdiagnostic mechanism that contributes to the aforementioned pathologies. Hence, we postulate that psychedelic-induced effects on mitochondria partially underlie their transdiagnostic benefits. Based on this assumption, we propose new treatment indications for psychedelics and that the health benefits induced by psychedelics depend on patient-specific mitochondrial dysregulation.

Keywords

Mitochondria, psychedelics, serotonin, transdiagnostic, bioenergetics

Introduction

For thousands of years, psychedelic drugs have been used for therapeutic purposes to induce perceptual changes and altered states of consciousness (Hofmann and Ott, 1980). These psychoactive effects of serotonergic psychedelics such as lysergic acid diethylamide (LSD), 4-phosphoryloxy-*N,N*-dimethyltryptamine (psilocybin, present in mushrooms of the genus *Psilocybe*), 3,4,5-trimethoxyphenethylamine (mescaline), or *N,N*-dimethyltryptamine (DMT) are mainly mediated by the 5-hydroxytryptamine (serotonin) 2A (5-HT_{2A}) receptor (López-Giménez and González-Maeso, 2018; Nichols, 2016; Vollenweider and Preller, 2020). Nevertheless, serotonergic psychedelics show very diverse interaction patterns with different classes of receptors, including several other 5-HT receptors (e.g., 5-HT_{1A}, 5-HT_{2B} and 5-HT_{2C}) (Halberstadt, 2015; Nichols, 2016; Ray, 2010). Many other 5-HT_{2A} receptor agonists are known, such as 2,5-dimethoxy-4-iodoamphetamine (DOI), which is less commonly used in humans but frequently used in animal studies (e.g., Fanibunda et al., 2019).

Transdiagnostic benefits of psychedelics

Stimulation of the 5-HT_{2A} receptor leads to profound acute effects on perception, affect and cognition (Dos Santos et al., 2021). In the late 1960s to early 1970s, the substances were first applied to treat patients with mood disorders, anxiety and substance use disorders (Dos Santos and Hallak, 2020). The results of these early studies suggested fast and enduring symptom reduction through psychedelic-assisted psychotherapy, a broad spectrum of methods that integrate the use of 5-HT agonists (e.g., LSD, psilocybin, DMT) with different non-pharmacological, psychological approaches (e.g., music, psychological support or psychodynamic psychotherapy) (Schenberg, 2018). After several years of prohibition of serotonergic psychedelics, research with the substances has recently regained broad interest and attention (Liechti, 2017).

In the second wave of research, studies aimed to reveal effects of psychedelics with and without psychotherapy on a wide range of pathologies including psychopathologies, cardiovascular, metabolic, neurological, and immunological pathologies. Most robust evidence for health benefits of psychedelics

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has been shown for depression (Carhart-Harris et al., 2016, 2018, 2021; Galvão-Coelho et al., 2021; Nygart et al., 2022; Palhano-Fontes et al., 2019), anxiety in life-threatening diseases such as cancer (Gasser et al., 2015; Griffiths et al., 2016; Grob et al., 2011; Ross et al., 2016), substance use disorders (Bogenschutz et al., 2015; Garcia-Romeu et al., 2014; Johnson et al., 2014, 2017; Thomas et al., 2013), and obsessive-compulsive disorder (Moreno et al., 2006). First studies also point to positive effects of serotonergic psychedelics in functional neurological disorders (Butler et al., 2020) and eating disorders (Renelli et al., 2020; Spriggs et al., 2021). Interestingly, within such diagnostic categories of disorders, different types of symptoms have been improved, even those that were not the primary target (Breeksema et al., 2020; Carhart-Harris et al., 2021). For example, in a study comparing psilocybin with escitalopram in patients with long-standing depression, not only depressive symptoms but also anxiety symptoms improved (Carhart-Harris et al., 2021). Similarly, in qualitative studies, patients frequently reported beneficial effects of psychedelics beyond the psychiatric symptoms that were defined as the target of the treatment (Breeksema et al., 2020). While the results are promising, current evidence is based on qualitative studies, observational studies, uncontrolled interventional studies and a limited number of randomized-controlled clinical studies (Carhart-Harris et al., 2021; Galvão-Coelho et al., 2021). No evidence-based guidelines exist on how to combine psychedelic use with behavioural interventions, while the field is currently developing (Brennan and Belser, 2022). Furthermore, it is important to take into consideration that all patients enrolled in clinical trials are carefully screened and many individuals potentially at risk for adverse outcomes are excluded (Bender and Hellerstein, 2022).

In addition to the effect on psychopathology, observational cross-sectional evidence points to a beneficial effect of psychedelics on hypertension (Simonsson et al., 2021a), obesity (Simonsson et al., 2021c), heart disease and diabetes (Simonsson et al., 2021b). Mostly based on evidence from animal studies and basic research, psychedelic-induced therapeutic value has been proposed for asthma, irritable bowel syndrome, rheumatoid arthritis, atherosclerosis, disorders of consciousness, migraine and Alzheimer's disease (Flanagan and Nichols, 2018; Kozlowska et al., 2022; Schindler et al., 2021; Scott and Carhart-Harris, 2019; Szabo, 2015; Thompson and Szabo, 2020; Vann Jones and O'Kelly, 2020). Taken together, most compelling evidence indicates benefits in a range of psychopathologies, while preliminary evidence hints towards effects on cardiovascular, metabolic, neurological and immunological pathologies. A meta-analysis and review on adverse events of serotonergic psychedelics found a very low occurrence of serious adverse effects (e.g., psychotic episodes), especially in modern clinical trials that exclude patients with predispositions for psychotic illnesses (Goldberg et al., 2020; Schlag et al., 2022). Commonly observed are transient adverse events such as headache, anxiety, nausea and increased blood pressure (Goldberg et al., 2020; Schlag et al., 2022).

Despite promising evidence on transdiagnostic benefits of psychedelics, the mechanisms that underlie these potentially long-lasting effects are still a matter of debate (Inserra et al., 2021; Vollenweider and Preller, 2020). In the next section, we introduce a mitochondrial view on psychedelics' transdiagnostic effects (see Figure 1). Our model introduces a systemic perspective focusing on the subcellular level of functioning of different kinds of organs, which contrasts with most other models that are brain-centred and focus on higher-level functions (Inserra et al., 2021; Vollenweider and Preller, 2020).

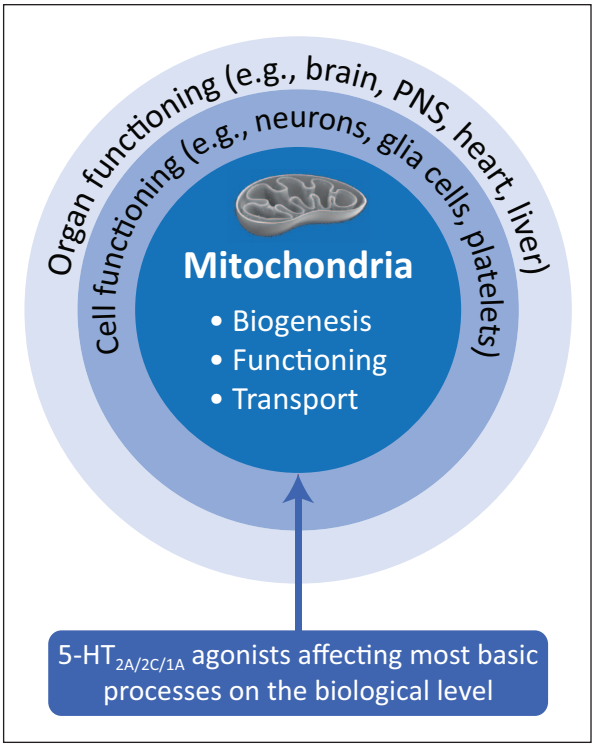

Figure 1. Mitochondrial model of serotonergic psychedelics' transdiagnostic effects. In this systemic perspective, we propose that psychedelics affect mitochondria (subcellular functioning), which in turn improves higher-level functioning (e.g., cell and organ functioning). Changes in multiple domains of higher-level functioning have the capacity to induce transdiagnostic effects.
PNS: peripheral nervous system.

Mitochondrial model of serotonergic psychedelics' transdiagnostic effects

We propose that serotonergic psychedelics induce transdiagnostic effects by changes in mitochondria as a subcellular mechanism, which in turn affects higher-level functioning on the cellular and organ levels (see Figure 1). As mitochondrial dysregulation plays an important role in psychological, metabolic, cardiovascular, neurodegenerative, endocrine, and immunological pathologies (Allen et al., 2018; Fissler et al., 2022; Geary, 2018; Holper et al., 2019; Karabatsiakis et al., 2014; Wallace, 2013; Zinovkin and Zamyatnin, 2019), we propose that psychedelic-induced mitochondrial effects at least partially mediate the health improvements induced by psychedelics in these pathologies. In the following, we review the effects of serotonergic psychedelics and other 5-HT agonists on mitochondrial biogenesis (increase of mitochondrial mass), functioning (the process and efficiency of energy production) and transport (migration of mitochondria within and between cells) in the brain and in the periphery in humans and animals.

Psychedelic-induced effects on mitochondrial biogenesis

Mitochondrial homeostasis in a cell is maintained through mitochondrial biogenesis, fission, fusion and mitophagy (Popov, 2020). Mitochondrial biogenesis is a complex biological process to increase mitochondrial mass, which leads to an increase in oxidative phosphorylation capacity, the reduction of pathological oxidative stress and the repair of mitochondria-associated dysregulation (Cameron et al., 2017). In response to cellular energy demands, the transcription factors that stimulate or inhibit mitochondrial biogenesis are up- or downregulated (Popov, 2020). These intracellular signalling pathways are mainly coordinated by the two master regulators of mitochondrial biogenesis: peroxisome proliferator-activated receptor γ coactivator-1α (PGC-1α) and sirtuin 1 (SIRT1) (Fanibunda and Vaidya, 2021; Kelly and Scarpulla, 2004).

The effects of 5-HT receptor agonists on mitochondrial biogenesis have been sparsely investigated in humans so far. One study showed the increase of mitochondrial biogenesis in human breast cancer cells after treatment with serotonin (Sola-Penna et al., 2020). This effect was blocked by ketanserin, a 5-$HT_{2A/2C}$ antagonist, suggesting that 5-HT_{2A} or 5-HT_{2C} receptor activation mediate mitochondrial biogenesis in human breast cancer cells.

Several animal studies investigated the effect of a 5-HT_{2A} receptor agonist on mitochondrial biogenesis in rodents. The first study measured mitochondrial biogenesis and PGC-1α transcription in normal rat kidney epithelial cells. The cells were treated with DOI for 24 h, which acts as a 5-HT_{2A} receptor agonist. Fluorescence microscopy showed an approximately twofold increase in MitoTracker™ staining, suggesting that DOI induces mitochondrial biogenesis in rat kidney cells (Rasbach et al., 2010). Furthermore, they reported an upregulation in PGC-1α expression in renal proximal tubular cells of rabbits after treatment with DOI, which was attenuated when pretreated with a pan-5-HT receptor antagonist. This suggests that the effect of DOI on PGC-1α and subsequently mitochondrial biogenesis is mediated by 5-HT receptors. In line with these findings, Harmon et al. (2016) found evidence for increased mitochondrial biogenesis through 5-HT_{2A} agonism in mouse kidney cells.

Another animal study investigated the effects of the 5-HT_{2A} receptor agonists DOI and lisuride on mitochondria in the rat neocortex (Fanibunda et al., 2019). The animals received 2 mg/kg DOI four times every 24 h. Analyses were conducted 2 h after administration of the last dose. The effect of lisuride was tested in vitro with rat cortical neuron cultures. Both the hallucinogenic DOI and non-hallucinogenic lisuride led to an increase in mitochondrial DNA content, a marker of mitochondrial biogenesis (Popov, 2020). Furthermore, this study showed the involvement of the SIRT1-PGC-1α axis that subsequently promotes mitochondrial biogenesis, since the effect on mitochondrial biogenesis did not appear in SIRT1 knockout mice (Fanibunda et al., 2019). Taken together, convergent evidence from human and animal studies in breast cancer, kidney and neocortex cells indicates an increase in mitochondrial biogenesis through 5-$HT_{2A/2C}$ agonism.

Furthermore, other studies have investigated the effects of non-hallucinogenic 5-HT receptor agonists on mitochondrial biogenesis. Several studies showed that stimulation of the 5-HT_{1F} receptor induces mitochondrial biogenesis in in vitro experiments with human kidney cells (Dupre et al., 2019), in vitro studies with kidney cells from rabbits (Garrett et al., 2014) and in vivo studies with mice (Garrett et al., 2014; Simmons et al., 2020, 2021). Also the 5-HT_{2B} receptor was found to be involved in mitochondrial biogenesis induced by in vitro treatment of mouse cells with serotonin (Nebigil et al., 2000).

Psychedelic-induced effects on mitochondrial function

Two major metabolic pathways provide energy for eukaryotic cells: anaerobic glycolysis and aerobic oxidative phosphorylation (OXPHOS) respiration. First, in glycolysis, one glucose is converted into two pyruvate, resulting in the anaerobic biosynthesis of adenosine triphosphate (ATP). Depending on the level of oxygen availability within the cell, pyruvate is converted into lactate (anaerobic glycolysis) or acetyl coenzyme A, which is then transported into the mitochondria matrix where it takes part in the Krebs cycle and oxidative phosphorylation. During oxidative phosphorylation, the electron-transport chain generates energy that is used to produce most of the cell's ATP (Alberts et al., 2002). Rasbach et al. (2010) found an approximately 45% increase in intracellular ATP in renal proximal tubular cells of rabbits after treatment with 10 μM DOI for 24 h. Similarly, DOI treatment in rat neocortex cells resulted in increased oxygen consumption rate, enhanced mitochondrial maximal and spare respiratory capacity, higher oxidative phosphorylation efficiency, resulting in elevated cellular ATP levels. Interestingly, these effects could not be replicated using SIRT1 knockout mice, implicating that the effects of 5-HT_{2A} receptor stimulation on mitochondrial biogenesis and function were mediated via SIRT1 (Fanibunda et al., 2019).

In line with these findings, results from a meta-analysis in rodent models showed that antagonists of 5-HT_{2A} receptors have inhibitory effects on mitochondrial complex I, which is the first enzyme of the eukaryotic electron-transport chain and a major contributor to the proton motive force, the driving force of ATP synthesis (Holper et al., 2019).

Furthermore, a robust pro-survival effect on cortical neurons was found after administration of DOI when challenged with oxidative and excitotoxic stress (Fanibunda et al., 2019). Similarly, Rasbach et al. (2010) found an increased recovery rate of cellular respiration in renal tubular cells of rabbits, when DOI was added after oxidant injury. However, they did not find a protective effect when DOI was applied 24 h before the oxidant injury to the cells (Rasbach et al., 2010).

Moreover, there is evidence for the effects of non-hallucinogenic 5-HT receptor agonists on mitochondrial function. For instance, a study by Nebigil et al. (2003) showed (in vitro and in vivo with 5-HT_{2B} receptor knockout mice) that the 5-HT_{2B} receptor plays a role for mitochondrial function and structure in heart cells and exerts cytoprotective effects in cardiomyocytes. Furthermore, the in vitro treatment of cortical rat neurons with serotonin resulted in an increase in ATP levels, which was prevented by pre-treatment with a 5-HT_{2A} receptor antagonist (Fanibunda et al., 2019). Enhanced ATP levels could also be found in vivo after delivering 5-HT directly into the neocortex of rats using osmotic minipumps (Fanibunda et al., 2019).

This evidence on increased mitochondrial function and ATP levels from animal studies is in line with one human study. A global increase in brain glucose metabolism of around 20% was found in healthy adults 90 min after administration of a 15 or

20 mg dose of psilocybin as measured with FDG-PET (Vollenweider et al., 1997). An increase in glucose metabolism could be a sign of higher ATP production through both increased anaerobic glycolysis and OXPHOS. Further research on possibly simultaneous contribution of anaerobic and aerobic ATP production in the brain needs to be conducted to shed more light onto the effects of serotonergic psychedelics on mitochondrial energy production. Neuronal activity depends on ATP, which is directly linked with neuronal glucose uptake (Iben et al., 2015). Taken together, several animal studies indicate that 5-HT receptor agonists enhance mitochondrial ATP production, which is in agreement with a human study showing increased glucose uptake.

Psychedelic-induced effects on intra- and intercellular mitochondrial transport

Mitochondria are highly mobile organelles, a property that allows them to relocate to the cell region with the highest metabolic demands (Boldogh and Pon, 2007; Mironov, 2007). In neurons, the transport of mitochondria to their needed location is crucial for optimal brain functioning (MacAskill and Kittler, 2010). Mitochondrial movement has been shown to increase in areas with high concentrations of ATP, while it decreased in the proximity of synapses with increased adenosine diphosphate (ADP) levels (Mironov, 2007). This suggests that ATP depletion, signalled by ADP production, might recruit mitochondria, while high levels of ATP might stimulate mitochondria to relocate within the cell (Mironov, 2007). The exact signals that regulate mitochondrial transport are still poorly understood, but one of them appears to be serotonin (Chen et al., 2007). 5-HT_{1A} receptor activation has been shown to stimulate mitochondrial movements in rat hippocampal neurons in vitro, while administration of a 5-HT_{1A} antagonist inhibited such movement (Chen et al., 2007). As serotonergic psychedelics such as LSD, psilocybin, DMT, and 5-MeO-DMT are also 5-HT_{1A} receptor agonists (Inserra et al., 2021; Nichols, 2016), we propose that they might elicit intracellular transport of mitochondria through 5-HT_{1A} stimulation.

As demonstrated in multiple recent studies, mitochondria can be moved not only within cells, but between cells as well, with the horizontal cell-to-cell mitochondrial transport being observed both in vivo and in vitro under different pathological conditions (Liu et al., 2021). Transport of mitochondria between donor and recipient cells can happen via the following mechanisms: through tunnelling nanotubes, extracellular vesicles, cell fusion, dendrites, and extrusion and internalization of free mitochondria (Liu et al., 2021; Torralba et al., 2016). Currently, to our knowledge, no evidence showed effects of psychedelics on intercellular mitochondrial transport. One potential but highly speculative mechanism through which psychedelics may affect this process is through astrocytes, which can be used as a donor of mitochondria (Hayakawa et al., 2016; Liu et al., 2021). It has been shown that 5-HT_{2A}-expressing excitatory neurons are activated by psychedelics and recruit astrocytes in the medial prefrontal cortex and somatosensory cortex (Martin and Nichols, 2016).

Psychedelics, mitochondria and energy-related sensations

We define sensations as all phenomenological states or all subjective experiences that are within the present stream of consciousness (‘mental workspace’ or ‘qualia’ are synonyms). Examples for complex, categorical, higher-level sensations are emotional feelings (such as sadness and happiness) or cognitive processes (such as remembering or reasoning). These higher-order sensations are composed of many lower-level sensations such as visual, auditory, olfactory or bodily experiences (Nummenmaa et al., 2018). Energy-related sensations include the sensation of fatigue (synonyms: exhaustion, weariness) and of energy (synonyms: vigour, vitality) (Filippi et al., 2022). These sensations can refer to different domains, such as physical, cognitive, emotional, social, motivational and sexual fatigue or energy sensations (Filippi et al., 2022). Importantly, mounting evidence suggests that mitochondrial bioenergetics underlie the sensation of energy and fatigue (Filippi et al., 2022; Filler et al., 2014; Karabatsiakis et al., 2014).

In line with the mitochondrial model of the transdiagnostic effects of serotonergic psychedelics, increases in acute and post-acute energy-related sensations after psychedelic drug use are described in qualitative studies, and the first quantitative evidence was found recently (Carhart-Harris et al., 2021; Szigeti et al., 2021). Pahnke (1969) introduced the term psychedelic ‘afterglow’ as a state of elevated and energetic mood. The psychedelic afterglow kicks in after the acute effects have subsided and gradually declines after a period of between 2 weeks and a month (Majić et al., 2015). In addition, during high-dose treatments, states of ego dissolution are often coupled with perception of ‘pure, formless energy and light’ (Glowacki et al., 2020), whereas in low- or even micro-dose treatments, perceptions of general increase in fluid thinking and mental energy are common (Johnstad, 2018). Patients with depression often describe the psychedelic-induced switch from an energy-deficient to an energy-rich state by metaphors such as ‘lifting up a veil’, ‘rising above the clouds’, ‘emerging from the dark’ and ‘getting rid of mental fog’ (Johnstad, 2018). Quantitative effects of psychedelics on energy-related sensations are sparsely investigated but hint to less fatigue – compared to escitalopram – and increases in sensations of energy in a microdosing study (Carhart-Harris et al., 2021; Szigeti et al., 2021). In addition, Orłowski et al. (2022) found increased positive emotional reactivity and reduced negative emotional reactivity in people using psychedelics. As positive affect is highly related to increased energy sensations and negative affect to fatigue sensations (Hinz et al., 2012), this finding hints to a higher energizability and lower fatigability through psychedelics (Filippi et al., 2022). Taken together, initial evidence suggests that energy-related sensations benefit from psychedelics (increased sensation of energy and reduced sensation of fatigue) and that energy-related sensations are a phenomenological correlate of mitochondrial bioenergetics (Filippi et al., 2022).

Model implications for transdiagnostic effects

We hypothesize that serotonergic psychedelics might benefit a wide range of pathologies with a mitochondrial aetiology. These disorders include psychological disorders (Allen et al., 2018; Anglin et al., 2012), migraine (Fila et al., 2019), Alzheimer’s disease (García-Escudero et al., 2013), obesity (Bournat and Brown, 2010), diabetes (Lowell and Shulman, 2005), hypertension (Lahera et al., 2017), cardiovascular diseases (Chistiakov et al., 2018), primary mitochondrial disorders (Chinnery, 2021),

multiple sclerosis (Witte et al., 2014), long COVID (Watanabe et al., 2022), chronic fatigue syndrome (Myhill et al., 2009), Parkinson's disease (Mandemakers et al., 2007), cancer (Boland et al., 2013), metabolic disorders such as phenylketonuria (Wyse et al., 2021), disorders of consciousness (Yu et al., 2021), autism (Haas, 2010), or age-related alterations such as sarcopenia or cognitive decline (Fissler et al., 2022; Holper et al., 2019; Wallace, 2013). In addition, a transdiagnostic perspective needs to model latent factors on different hierarchical levels of functioning (Fissler et al., 2022). This is necessary to understand which hierarchical level of functioning is affected by serotonergic psychedelics. Psychedelics might affect the highest level of cerebral functioning (c factor), lower-order factors such as the general psychopathological factor (p factor), the general intelligence factor (g factor), or subfactors of p and g such as internalizing symptoms or attention (Fissler et al., 2022; Ruggero et al., 2019).

Hence, from our mitochondrial model, recommendations can be derived with regard to disorders and outcomes that need to be investigated in future research. In addition, mitochondrial biomarkers could contribute to improving precision medicine. Mitochondrial dysregulation rather than the patient's disorder category may predict the efficacy of serotonergic psychedelics and other treatments. That means, two patients of different disorder categories (e.g., major depression and dementia) with a similar mitochondrial dysregulation profile might benefit from psychedelic use, while another patient with the same disorder category (e.g., major depression) but without this mitochondrial dysregulation will not. Thus, mitochondrial biomarkers may predict the efficacy of different treatments specifically tailoring psychedelic drug sessions, other pharmacotherapies and psychotherapy to patient's needs.

Limitations and future research

Until now, studies investigating the influence of 5-HT_1 and 5-HT_2 receptor agonists on mitochondrial biogenesis and function were mainly conducted using animal models. Therefore, the most important step is to investigate these mechanisms in humans. Dosing, administration frequency and application form are important in determining the effects and need to be considered in human studies. In the animal studies, the cells were exposed to the 5-HT_2 receptor agonists for 24 h or even 6 days (Fanibunda et al., 2019), whereas in clinical and research practice, patients usually receive one to three moderate-to-high doses of the psychedelic substance (Reiff et al., 2020). Effects of psychedelics on mitochondria could be measured via mitochondrial respiration measures from muscle cells (Gardner et al., 2003), platelets (Hroudová et al., 2013) and immune cells (Karabatsiakis et al., 2014), via measures of mitochondrial DNA content, or via magnetic resonance spectroscopy measures related to ATP production (Stork and Renshaw, 2005). New methodological advances such as hyperpolarized ^{13}C magnetic resonance imaging could reveal mitochondrial activity-related changes in whole-body glucose uptake through psychedelics (Badawi et al., 2019; Wang et al., 2019). Near-infrared spectroscopy (NIRS)-based measures of cytochrome *c* oxidase (CCO), complex IV of the electron-transport chain, could reveal psychedelic effects on mitochondrial function in the brain (Bale et al., 2016). Emerging techniques such as broadband NIRS allow the measurement of the oxidation state of CCO in the brain (de Roever et al., 2017). The determination of the absolute concentrations of the oxidized and reduced state of CCO has recently been developed as well (Hashem et al., 2021). Furthermore, in future research it is important to differentiate between increases in ATP production due to mitochondria (via oxidative phosphorylation) and anaerobic glycolysis. ATP generation by anaerobic glycolysis, which takes place outside mitochondria, may play an important role during brain activity and in response to cognitive tasks (Debatin, 2020).

In addition to evidence on psychedelic-induced effects on mitochondria, other biological processes that are reciprocally linked with mitochondria have been shown to be affected by psychedelics but were not a part of this perspective article. These reciprocally linked processes include inflammatory processes, oxidative stress, the autonomic nervous system, and the hypothalamic-pituitary-adrenal-axis activity (Picard et al., 2018; Varadarajan et al., 2022). Psychedelics may affect these biological processes via mitochondrial regulation and mitochondria may be indirectly affected by psychedelic-induced effects on these processes in turn (Picard et al., 2018). This crosstalk between mitochondria and other stress regulation systems is highly complex and requires further investigation.

Psychedelics acutely affect direct mitochondrial outcomes including mitochondrial biogenesis, function and possibly transport, but long-term effects on mitochondria are currently unknown. Future studies should investigate these long-term effects. Effects of psychedelics on energy-related sensations – a phenomenological correlate of mitochondrial bioenergetics (Filippi et al., 2022) – are sparsely investigated. First evidence hints to an afterglow period with reductions in sensations of fatigue and increases in sensations of energy but more research is needed. The effect of psychedelics on mitochondria might also hint to new potential contraindications. For example, subcellular mechanisms affected by 5-HT may have detrimental effects in case of patients with breast cancer (Sola-Penna et al., 2020).

In research and clinical practice, psychedelic use is often combined with behavioural interventions (e.g., acceptance and commitment therapy, cognitive behavioural therapy, psychodynamic psychotherapy, listening to music during the session) while an evidence-based guideline is lacking (Brennan and Belser, 2022). Currently, it is unclear how behavioural interventions could profit from or interact with psychedelic-induced effects on mitochondria. Effects on mitochondria-related sensations of energy (Filippi et al., 2022), intero- and exteroception (Picard, 2022) and neuronal plasticity (Cheng et al., 2010) could support psychotherapy and health behaviour changes (Knudsen, 2022; Teixeira et al., 2022). The interplay between psychedelics, psychotherapy and mitochondria needs to be investigated in future studies.

It is of importance to note that not only serotonergic psychedelics but also non-hallucinogenic 5-HT_{2A} agonists showed effects on mitochondria. Non-hallucinogenic 5-HT agonists may have similar therapeutic effects as serotonergic psychedelics (Cunningham et al., 2023) and comparable effectiveness should be investigated (Kaplan et al., 2022).

Lastly, the effects and mechanisms of action at the mitochondrial level of other serotonergic drugs, such as selective serotonin reuptake inhibitors (SSRIs) should be better elucidated (Emmerzaal et al., 2021). This could help to understand why

psychedelics may prove effective in instances where first-line pharmacological treatments do not (e.g., treatment-resistant depression). Evidence points to SSRIs having an impact on mitochondrial function, but the effects differ depending on the antidepressant (Emmerzaal et al., 2021; Fanibunda and Vaidya, 2021; Holper et al., 2019): Studies in rat models show both negative and positive effects on either or both complexes I and IV, depending on the type of SSRI (Emmerzaal et al., 2021; Holper et al., 2019).

Conclusion

Increasing evidence demonstrates that serotonergic psychedelics have transdiagnostic benefits on several psychological, metabolic, inflammatory, neurodegenerative, and cardiovascular pathologies that are linked to mitochondrial dysregulation. We propose a new mitochondrial view on transdiagnostic benefits of psychedelics. More specifically, psychedelic-induced effects on mitochondrial biogenesis, functioning and transport may partly mediate transdiagnostic effects of psychedelics. Clinically most important, our model generates new hypotheses about pathologies that profit from serotonergic psychedelics, and mitochondrial biomarkers may improve prediction of psychedelic treatment efficacy.

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