MIND FOUNDATION

The future of psychedelics in Alzheimer's disease treatment

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> *Among the potential targets for psychedelics in neurodegenerative diseases, neuroinflammation might be the most promising. Psychedelic researchers are gathering more information about how these compounds modulate different inflammatory processes.*

Evidence is mounting that psychedelic drugs like LSD, psilocybin, and DMT can be successfully used as treatments for mood disorders like anxiety and depression. Beyond psychological benefits, insight into their physiological mechanisms of action, including positive effects on neuroinflammation and neuroplasticity, has inspired a new wave of research. Researchers are now investigating whether psychedelic therapies can be administered more broadly, treating not only mood disorders but also neurodegenerative conditions like dementia and Alzheimer's disease. Will psychedelics usher in a more hopeful era for patients with neurodegenerative conditions? There are only two ongoing studies exploring the use of psychedelics for the treatment of Alzheimer's disease, and this article reviews the rationale behind them.

Alzheimer's: The disease and available treatments

With over 30 million global cases, Alzheimer's disease (AD) is one of the world's leading causes of cognitive decline. The disease causes cell and connectivity losses in the brain, and its progression leads to a loss of important mental skills, including working memory, attention, planning, and self-control.1 The causes of AD are complex and manifold. Specific genetic variants have been found to correlate with it, but they can't account for all cases of the disease in the population. Apart from mutations, lifestyle factors including diets rich in processed foods, physical inactivity, smoking, and drinking alcohol, as well as social isolation, have all been identified as risk factors.2

AD has been causally linked to the pathological aggregation of proteins that clump into *plaques* between nerve cells (amyloid-ß or Aß protein) or twist into fibres or *“neurofibrillary tangles”* within the cell itself (tau protein). The abnormal deposition of these proteins is particularly pronounced in the hippocampus (one of the brain’s main memory centres), as well as the cortex and the basal forebrain.3 Exactly how these molecules drive neurodegenerative processes has not been determined. So far, it can be said that excessive plaques and tangles may drive cell death by disrupting basic cell functioning such as the stress response or nutrient transport.4,5

The cholinergic hypothesis – the idea that AD is caused by the dysfunction in neuronal signalling via the neurotransmitter acetylcholine (ACh) – has long been the primary paradigm in developing AD treatments.3 Indeed, AD patients’ brain cells produce less of this neurotransmitter, causing cholinergic (ACh-containing) neurons to die.6 The majority of clinically approved drugs for AD work by stopping the degradation of Ach, and while they have been shown to be effective for improving cognitive function, they cannot fully stop the decline.6,7

The cholinergic hypothesis doesn’t address the underlying causes of AD – Aß plaques or neurofibrillary tangles of tau protein. There are currently no approved drugs targeting these structures, although many are in clinical trials or under review.7 However, scientists are also exploring other options: Many now focus on treating chronic brain inflammation and cellular stress.8

The inflammatory hypothesis of Alzheimer’s disease

A newly popularised way of looking at AD, as well as other neurodegenerative diseases such as Parkinson’s or multiple sclerosis, is a disease driven by chronic inflammation. In the last decade, it has become clear that the brains of AD patients exhibit a sustained inflammatory response.9 The main agents of this response are microglia. These are the brain’s mobile “cleaner” cells that constantly scavenge the brain for any sign of damaged cells, infectious agents, or indeed plaques such as the ones formed by Aß. When they encounter such threats, they get rid of them by ingesting and degrading them. In addition to ‘’eating” inflammation-promoting material, they also secrete many different chemicals that serve as inflammatory signals to the rest of the immune system and draw more cleaner cells to plaque sites.

Inflammation in the brain makes virtually every aspect of AD worse, including its pathogenesis.9 Some of the molecules secreted by microglia cause chemical changes in the tau protein and worsen neurofibrillary tangles. And Aß is inextricably related to the immune response: during healthy ageing, it contributes to non-pathological inflammatory responses and gets cleared by microglia afterwards. In AD patients, more Aß is produced—possibly due to more inflammation in the brain from the start)—and microglia become less able to clear it. Inflammation also worsens the symptoms and progression of AD: it impairs learning and memory and reduces synaptic plasticity (the ability of neurons to modify their connections).10

The role of serotonin in Alzheimer’s disease

AD research has mainly focused on the role of the acetylcholine system because much of the disease progression can be attributed to the loss of acetylcholine signalling and the death of cholinergic neurons. But do other neurotransmitters matter?

It is now becoming increasingly apparent that changes in serotonin signalling might worsen cholinergic deficits in AD progression.8 Serotonin is one of the most abundant neurotransmitters in the brain, and it is found in neurons co-localising with cholinergic neurons in the cortex and hippocampus, where they are thought to regulate each other’s function. In the brain stem, AD patients show a major loss of serotonergic neurons,

corresponding to a more severe progression of the disease.11 Furthermore, SSRI-antidepressants, which modulate the amount of available serotonin in the brain, have been shown to decrease the symptoms of memory impairment in neurodegenerative diseases, as well as to decrease microglia-mediated inflammatory responses.12,13

New research has shown that classical psychedelics such as LSD and psilocybin may be effective in the treatment of depression and anxiety.14 There are currently several clinical trials underway which test LSD and psilocybin, as well as DMT and ayahuasca (a DMT-containing brew) as treatments for these and other psychiatric conditions. Like SSRIs, psychedelics are serotonergic drugs, meaning they exert their effects by primarily affecting the serotonin system. Yet, both of these classes of drugs do more in the brain than just change serotonergic signalling. Extensive research in cell culture and animals has shown that 5HT-2A agonists (compounds that interact with the serotonin 5HT-2A receptor, including most prominently LSD and psilocybin) have anti-inflammatory effects.15 In humans, a recent study has shown that low doses of LSD increase the blood plasma levels of BDNF, a molecule implicated in neuroplasticity.16 Does this mean that psychedelics could be as effective as SSRIs in AD symptom treatment, on both a psychological and physiological level?14 And since SSRI treatment often leads to negative side-effects (including chronic fatigue, weight gain, and sexual dysfunction),17 what would it mean if there was a group of drugs that act similarly on the serotonin system, but with fewer acute side-effects?18

Neurodegenerative disease as a new question in psychedelic research

In the last decade, evidence has mounted that psychedelic drugs can have positive physiological effects. It didn't take long for the discovery of the anti-inflammatory effects of 5HT-2A agonists15 to inspire researchers to examine psychedelic compounds as potential medicines against neurodegeneration. As of 2021, there are two ongoing studies probing the potential of psychedelics in AD and in cases of mild cognitive impairment.

Eleusis, a company researching the therapeutic benefits of psychedelics, is currently conducting a clinical trial investigating the effects of low-dose LSD ("microdosing") in Alzheimer's patients. They are building up on recently published results of a Phase I trial in which they demonstrated that repeated microdosing (21 non-consecutive days) is well tolerated with minimal adverse effects in healthy volunteers.19 These findings allowed Eleusis to move on to Phase II, where they are examining the effects of LSD microdoses on AD patients.

In the US, Johns Hopkins University has been one of the pioneering institutions in the research of psychedelic therapies for mental health conditions. Their Center for Psychedelic and Consciousness Research has recently started a study investigating whether psychedelic-assisted therapy can help treat depression in people with AD – a disorder that commonly co-occurs with the disease, estimated to affect almost 40% of AD patients.1However, knowing that psychedelics have positive effects on neuroplasticity and neuroinflammation, might they help with more than just depression?

What can psychedelics do to help?

Eleusis have recently published white papers detailing the scientific background of their ongoing LSD trial for AD. Around the same time, a review paper was published in *Frontiers in Synaptic Neuroscience* explaining why researchers have become interested in psychedelics as a means of treating neurodegenerative disease.20 What is their rationale? The main mechanisms suggested by both groups of researchers can be grouped into three main categories.

Psychedelics reduce inflammation in the brain. 5HT-2A receptor agonists act as potent anti-inflammatory agents, mostly by reducing cellular stress and modulating the activity of pro-inflammatory molecules, such as those secreted by microglia (although research directly on microglia is yet to be conducted).20,21

Psychedelics might affect neurogenesis and neuroplasticity. The loss of neurons and the connections between them has been linked to all symptoms of AD. It is unclear whether psychedelics might reverse or exacerbate some of these processes. In rat models, large doses of 5HT-2A agonists like psilocybin and LSD inhibit the growth of new neurons in the hippocampus (the area of the greatest importance for neuron loss in AD).22 On the other hand, another rat study demonstrated that low doses inhibit cell death in this brain region.23 From this, it is unclear whether the net effect in humans would be positive or negative. Apart from neuron growth, however, a number of psychedelics have been found to enhance neural connectivity. Studies in cultured human cells treated with different psychedelic compounds demonstrated growth of the projections that receive signals from other neurons (dendrites), as well as increased numbers of connective junctions with other neurons (synapses).24

Can psychedelics improve learning and memory? Treatments that reduce cognitive decline are among priorities for intervention in neurodegenerative diseases. Presently, no studies have conclusively demonstrated that 5HT-2A agonists can significantly improve cognition, although data on this matter are limited. While many users of recurrent low-dose psychedelics (microdosing) claim this practice enhances their memory, studies so far have found no memory benefits of LSD and psilocybin at these doses.19,25,26 However, as the researchers point out – ‘’While these results contradict reports of enhanced cognition in the context of recreational use, it should be noted that not all pharmaceutical drugs that target cognitive and behavioural impairments have nootropic [*cognitive-enhancing*] effects on healthy participants.”19

The brain and the mind in Alzheimer’s disease

Promising as psychedelics may be, we know of no medicine that can regrow dead neurons. Psychedelic therapies are unlikely to cure AD, and since their mechanisms of action are not primarily directed at the most important systems of AD pathogenesis, their physiological benefits will likely be limited. However, as they show exceptional promise for mental health conditions, they are not to be discounted as potential aids in the treatment of neurodegenerative diseases and particularly their psychological comorbidities. More so, neurodegeneration and mental health may be linked even beyond depression as a side-effect of AD. Mindfulness training has been shown to benefit early-stage AD patients’ mental health by reducing depression and stress, but also their physical health by reducing neuroinflammation.27 Many of the benefits of mindfulness can be provided by psychedelics, and these two methods of intervention are thought to complement one another well.28

Among the potential targets for psychedelics in neurodegenerative diseases, neuroinflammation might be the most promising. Psychedelic researchers are gathering more information about how these compounds modulate different inflammatory processes. With time, this may enable scientists to maximise the potential of psychedelic drugs in a variety of therapeutic contexts. This research can go in the direction of optimising the dosing protocols in terms of frequency and concentration, but also in the direction of biochemical studies exploring other compounds and receptors.

Psychedelics don’t end with psilocybin and LSD. Other molecules, including popular and naturally occurring ones like DMT, but also completely novel synthetic molecules, may play a future role in the treatment of mental disorders and neurodegenerative diseases. In addition to its positive effects on mental health,29 the immunoprotective and anti-inflammatory properties of DMT have been suggested in different studies,30 and there are indications that they may be mediated not by 5HT-2A, but by another, novel receptor, Sigma1. And,

in the increasingly rich world of synthetic psychedelic molecules, there are several that could serve as an interesting research focus. Some studies have already identified psychedelic molecules with anti-inflammatory properties stronger than those of LSD.15 Others have managed to isolate the locus of anti-inflammatory activity and generate psychedelic-like molecules that lose their mind-altering properties while maintaining the physiological benefits.31 In the future, these drugs may yet be recognised for their therapeutic qualities by psychiatrists and neurologists alike.

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