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REVIEW

Anderson: Ketamine and psychedelics in Alzheimer's

Ketamine and psychedelics: A path to Alzheimer's disease prevention?

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ABSTRACT

Astrocyte mitochondrial dysfunction contributes to mild cognitive impairment (MCI) and Alzheimer's disease (AD), making it a promising therapeutic target. This review investigates whether ketamine and psychedelics can modulate MCI and AD pathophysiology by regulating astrocyte mitochondria. Data on astrocyte metabolism, stress vulnerability, and interactions with other CNS cells, including neurons, are synthesized from literature searches in PubMed, Scopus, and Google. The reviewed literature indicates that reactive astrocyte-linked blood-brain barrier disruption, impaired glymphatic clearance, reduced glutamate uptake, decreased neuronal lactate supply, and synaptic loss can exacerbate neuronal and astrocyte amyloid-β accumulation and tau hyperphosphorylation. Developmental stressors and childhood trauma are an Alzheimer's disease risk factor that upregulates chronic cortisol exposure to compromise astrocyte mitochondrial resilience. Low-dose ketamine is proposed to act partly via inner mitochondrial membrane N-methyl-D-aspartate receptor (NMDAr). Psychedelics can engage the aryl hydrocarbon receptor (AhR), sigma-1-receptor, and serotonin 2A receptor (5-HT2AR). Ketamine and the psychedelics can also positively allosterically modulate the tropomyosin receptor kinase B (TrkB), including on the outer mitochondrial membrane to modulate mitochondrial calcium regulation. This is proposed to contribute to mitochondrial melatonergic pathway upregulation and associated increase in the mitochondria-derived peptide, humanin. These factors are proposed to support neuronal metabolism and mitigate inflammation and oxidative stress. However, their disease-modifying potential requires future experimental investigation. Overall, astrocyte mitochondrial regulation offers a testable framework for investigating ketamine and psychedelics in MCI and AD. Further experimental validation and controlled clinical trials are essential to establish safety and determine if these agents can slow disease progression or prevent onset.

Keywords: Alzheimer's disease, mild cognitive impairment, ketamine, psychedelics, treatment, astrocytes, mitochondria, melatonin, humanin, aryl hydrocarbon receptor.

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INTRODUCTION

There is a growing dissatisfaction at the lack of progress in the conceptualization and treatment of Alzheimer's disease, which seems stymied by the 40-year old perspective that emphasizes the roles of amyloid-β plaques and hyperphosphorylated tau (p-tau) associated tangles [1,2]. The growing bodies of data on the most recent anti-amyloid-β monoclonal antibodies (aducanumab, lecanemab and donanemab) indicate that they have very little efficacy in preventing cognitive decline in Alzheimer's disease, other than decreasing the slight disruption caused by amyloid-β accumulation within the CNS [3]. A recent comparative meta-analysis of these three monoclonal antibodies to amyloid-β with melatonin and exercise in suppressing cognitive decline in mild cognitive impairment (MCI) patients showed melatonin to have most efficacy, followed by exercise [4]. The beneficial effects of exercise on dementia are strongly determined by alterations in astrocyte and microglia function [5], whilst studies, over many decades, show melatonin to attenuate cognitive decline in dementia models [6-10].

As melatonin can be produced within the mitochondria of possibly all cells [11,12], this raises the possibility of targeting a local and more focussed upregulation of the mitochondrial melatonergic pathway at CNS sites under challenge in the course of MCI and the shift into Alzheimer's disease. Across diverse CNS conditions, there is a growing appreciation of the role of astrocytes in determining neuronal survival and function [13], including in Alzheimer's disease [14,15,16], Parkinson's disease [17,18] and amyotrophic lateral sclerosis [19,20]. As primary astrocytes and the C6 glioma cell line have long been shown to produce and release melatonin [21], with levels of melatonin efflux significantly regulated by the major genetic susceptibility gene for Alzheimer's disease, apolipoprotein (Apo)E4 [22], astrocytes would seem an interesting cell to investigate the regulation of the mitochondrial melatonergic pathway. Determining astrocyte mitochondrial melatonergic pathway regulation raises the possibility of targeting local astrocyte melatonin upregulation to suppress pathophysiological processes underpinning MCI and its progression.

Recent work indicates that low-dose ketamine may mediate its fast-acting antidepressant efficacy by upregulating astrocyte mitochondrial function, plausibly including the astrocyte mitochondrial melatonergic pathway and melatonin release, thereby optimizing mitochondrial function and dampening inflammation and oxidant production in the astrocyte's local microenvironment [12,17]. This is supported by data

showing ketamine: 1) to increase local melatonin production in preclinical models [23]; 2) to increase cyclic adenosine monophosphate (cAMP)/protein kinase (PK)A [24], which rapidly induces the initiating enzyme of the melatonergic pathway, aralkylamine N-acetyltransferase (AANAT) [25]; and 3) ketamine suppresses the pro-inflammatory dimer of Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), p65/p50, and upregulates the resolution associated NF-κB dimer (cRel/p50) to interact with Signal transducer and activator of transcription (STAT)3 to upregulate the melatonergic pathway, as shown in many types of human cells [26]. By enhancing mitochondrial function, any astrocyte-derived melatonin, with intracrine, autocrine and paracrine effects, would potentially attenuate the suboptimal mitochondrial function that is widely believed to underpin the emergence of many aging-associated conditions, including Alzheimer's disease [27].

This article reviews CNS processes modulated by ketamine and the possibly also fast-acting psychedelic antidepressants. Ketamine and psychedelics efficacy is proposed to be mediated via the optimization of astrocyte mitochondrial function, including by upregulating astrocyte mitochondrial melatonin and possibly the mitochondria-derived peptide, humanin, both of which have autocrine and paracrine effects to dampen inflammation and oxidant production as well as optimizing mitochondrial function in astrocytes and the cells of the astrocyte microenvironment, including neurons, microglia, oligodendrocytes, pericytes and endothelial cells [28,29]. In the CNS, humanin is predominantly released by astrocytes [30]. Ketamine effects in astrocytes arise from ketamine's amphiphilic properties, allowing ready access into cells and mitochondria [31]. Ketamine can also gain entry into neurons and astrocytes, including their mitochondria, via the organic cation transporters (OCT)1-3 [32,33]. Low dose ketamine optimizes mitochondrial function whilst also positively allosterically modulating the brain-derived neurotrophic factor (BDNF) receptor, tropomyosin receptor kinase (Trk)B [34], a long recognized trophic target for Alzheimer's disease treatment [35].

First, low-dose ketamine effects on CNS processes are briefly reviewed, and then linked to Alzheimer's disease pathophysiology. Processes regulated by psychedelics are then briefly reviewed and overlapped with those of ketamine, including in regulating

Alzheimer's disease pathophysiology. Future research directions and treatment implications are then detailed.

MATERIALS AND METHODS

The following terms were searched on Medline/PubMed, Scopus and Google: 'ketamine', 'psychedelics', 'Alzheimer's disease,' 'developmental stress/trauma', 'mitochondria', 'Alzheimer's disease treatment', 'astrocytes', 'microglia', 'oligodendrocytes', 'BDNF', 'TrkB', 'melatonin', 'opioidergic system', 'lactate', 'lactate shuttle', 'oxytocin', '5HT2A receptor', 'sigma-1-receptor', 'mitochondria-associated membranes', 'NMDA receptor', 'inner mitochondrial membrane NMDAR', 'glymphatic system', 'cortisol', 'HPA axis', 'glucocorticoid receptor', to provide the background data for this article.

KETAMINE'S MODULATION OF CNS PROCESSES

Although originally developed as a horse tranquilizer and used as an anaesthetic and recreational drug, low dose ketamine/esketamine and its active metabolites, norketamine and hydroxynorketamine (HNK), have proven utility as fast-acting antidepressants [36]. As well as antidepressant and anti-suicidal effects, ketamine also has pro-cognitive effects in treatment-resistant depression, significantly improving processing speed, working memory, and executive control, as shown in a recent systematic review [37]. Ketamine's rapid antidepressant and pro-cognitive effects have classically been attributed to ketamine's non-competitive antagonism of the post-synaptic N-methyl-d-aspartate receptor (NMDAr) [38,39]. Ketamine gains entry into cells either via its amphiphilic properties and/or via its uptake by OCT1 and/or OCT3, both of which are expressed in neurons, whilst OCT3 is also expressed in astrocytes [31,32]. Once inside cells, ketamine blocks the NMDAr pore from the inside, which in neurons leads to α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor upregulation, thereby lowering toxic levels of Ca^{2+} entry into the post-synaptic neuron [40,41]. Classically, the antidepressant efficacy of ketamine has been attributed to its effects at specific neuronal NMDAr subunits (NMDAr-NR2D), whilst its psychotomimetic effects are proposed to be mediated via different neuronal NMDAr subunits (NMDAr-NR2A/2B) [42]. Ketamine's primary mode of efficacy is therefore contained in a classical neuroncentric conceptualization of brain function.

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Recent work indicates that low-dose ketamine's antidepressant effects are mediated via the modulation of mitochondrial function, involving the upregulation of local adenosine [43], which can act on the mitochondrial adenosine A3 receptor (A3r) to optimize mitochondrial function, oxidative phosphorylation (OXPHOS) and ATP production [44]. These authors also propose that ketamine's modulation of the neuronal NMDAr mediates its psychotomimetic effects [43]. This work therefore shifts the core processes of ketamine efficacy from neuronal to mitochondrial function, with other correlates of ketamine efficacy downstream from its regulation/optimization of mitochondrial function.

Recent work has re-conceptualized ketamine's mode of efficacy, proposing that it arises from entry into astrocytes at the blood-brain barrier (BBB), where its amphiphilic nature leads to the unavoidable entry into the astrocytic end-feet that extensively cover brain capillaries [28]. Although this may lead to the inhibition of the astrocyte plasma membrane NMDAr, with implications for mitochondria redistribution in astrocytes to glutamate extra-synaptic spillover [45], it is likely that ketamine has stronger direct effects on astrocyte mitochondria. As mitochondria express an NMDAr on the inner mitochondrial membrane that has long been appreciated to modulate mitochondrial function and wider ionic regulation [46,47], low-dose ketamine is proposed to regulate the mitochondrial inner membrane NMDAr, leading to wider ionic regulation that culminates in a small increase in mitochondrial Ca^{2+} influx that optimizes astrocyte mitochondrial function [28]. As noted, ketamine may directly activate the BDNF receptor, TrkB, and/or positively allosterically modulate TrkB [48]. As well as being plasma membrane located, TrkB can also be expressed on the mitochondrial outer membrane where it regulates ionic flux [49]. Ketamine may therefore have two mitochondrial receptor sites to directly modulate astrocyte mitochondria function and ionic regulation.

Ketamine can also indirectly modulate mitochondria via nuclear transcription regulation of mitochondrial function e.g. via ketamine's positive allosteric modulation of plasma membrane TrkB to increase cAMP response element-binding protein (CREB). which upregulates Peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), the master regulator of mitochondrial biogenesis [50], thereby upregulating the nuclear transcription of mitochondrial respiratory chain components and transcription factors (such as transcription factor A, mitochondrial

[TFAM]) [51]. Consequently, ketamine effects on nuclear regulation of mitochondria can contribute to mitogenesis, optimized OXPHOS, and enhanced respiratory efficiency [51]. As noted, ketamine also increases cAMP [24] that upregulates plasma membrane TrkB expression [52], with cAMP/PKA also increasing the melatonergic pathway [25], including N-acetylserotonin (NAS). NAS, the immediate precursor of melatonin, is a BDNF mimic that activates TrkB [53], whilst NAS also increases BDNF [54]. Ketamine, therefore, has a number of routes for upregulating TrkB levels and activation. Aryl hydrocarbon receptor (AhR) activation, predominantly via increased cytochrome P450 (CYP)1B1 and CYP1A2 can *O*-demethylate melatonin to NAS to further increase NAS, TrkB activation and BDNF induction [55]. Interestingly, PGC-1α has negative reciprocal interactions with inflammatory NF-κB p65/p50 [50], suggesting an association of ketamine/TrkB/cAMP/CREB/ PGC-1α with melatonergic pathway induction, given the suppression of the melatonergic pathway by the NF-κB p65/p50 dimer via interactions with STAT3, across diverse human cell types [26]. The direct and indirect actions of ketamine on mitochondrial function are shown in figure 1.

Low dose (typically 0.5 mg/kg; 40-minute I.v. infusion) ketamine's antidepressant effects have also been modeled as arising from increased β-endorphin activation of the μ-opioid receptor due to its capacity to increase hypothalamic pro-opiomelanocortin (POMC), the precursor of β-endorphin [56]. Ketamine, via the proposed increase local, non-pineal, melatonin [23], can also upregulate β-endorphin [57], suggesting that ketamine's upregulation of β-endorphin and enhanced activation of the μ-opioid receptor may be partly downstream from its proposed induction of the mitochondrial melatonergic pathway. As noted in the Introduction, ketamine's capacity to induce the mitochondrial melatonergic pathway is indicated by its rapid upregulation of cAMP/PKA pathway [24], which induces the initiating enzyme of the melatonergic pathway, AANAT [25], whilst ketamine also modulates the transcription factors, STAT3 and NF-κB, which interact (dependent upon NF-κB dimer composition) to either up- or down-regulate the melatonergic pathway, as shown across diverse human cell types [26]. Such data indicate that ketamine entry into astrocytes may have a couple of routes by which it upregulates the astrocyte mitochondrial melatonergic pathway, with both NAS and melatonin potentially contributing to ketamine's CNS effects.

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The optimization of previously challenged mitochondrial function in astrocytes is proposed to underpin ketamine's antidepressant efficacy, including by re-establishing the BBB and debris collection by the glymphatic system as well as upregulating the excitatory amino acid transporters (EAATs) to attenuate glutamate-driven excitotoxicity and increase lactate as an energy substrate for neurons, whilst also preventing reactive astrocyte induced synapse elimination [28]. Clearly, such proposed astrocyte-derived anti-depressant processes are highly relevant to the pathophysiological changes occurring in MCI and Alzheimer's disease [58,59].

ALZHEIMER'S DISEASE PATHOPHYSIOLOGY

As well as amyloid-β associated plaques and p-tau associated tangles, a plethora of diverse factors and processes have been proposed to contribute to cognitive loss in MCI and Alzheimer's disease. These include many astrocyte mediated processes [60], such as increased BBB permeability [61], decreased glymphatic system function [62], EAATs [63] and neuronal lactate provision [64] as well as dysregulated lipid droplet accumulation [65] and associated cholesterol dysregulation [66]. Interestingly, melatonin prevents/improves these deficits, including BBBp [67], glymphatic system [68], EAATs [69], lactate provision by decreasing astrocyte reactivity [28] and lipid droplet accumulation [70]. As does ketamine: BBBp [71], glymphatic system function [72], EAATs [73], astrocyte lactate [74] and lipid regulation [75]. Such overlaps of melatonin and ketamine effects plausibly arise from ketamine, via cAMP/PKA and/or STAT3/NF-κB induction of the melatonergic pathway [23].

Clearly future investigation is required to clarify ketamine's induction of the melatonergic pathway in astrocytes, including whether suppressors of the astrocyte melatonergic pathway, such as hyperglycemia-associated methylglyoxal, which binds tryptophan via protein-protein interactions to suppress tryptophan availability for the tryptophan-melatonin pathway [76], can thereby attenuating ketamine efficacy. This is indicated by a relatively suppressed antidepressant efficacy of low-dose ketamine in people with type 2 diabetes mellitus (T2DM)/metabolic syndrome, which is typically associated with hyperglycemia and raised methylglyoxal levels [77]. It therefore requires clarification whether the optimization of the astrocyte tryptophan-melatonin pathway may have to be first targeted to optimize subsequent ketamine efficacy e.g. by

the initial quenching of methylglyoxal by quercetin [78] prior to ketamine administration.

Currently, ketamine has only been trialed in the treatment of depression and agitation in MCI [79] and Alzheimer's disease patients [80], where it shows efficacy and tolerability, as reviewed in [80]. Previous data has highlighted the potential utility of ketamine in MCI/Alzheimer's disease management [81,82]. However, the investigation of ketamine utility on MCI and Alzheimer's disease pathophysiology has never been investigated. The proposed mode of efficacy in studies suggesting utility assume ketamine efficacy to be mediated via its non-competitive antagonism of the post-synaptic neuronal NMDAr and are therefore tied to a classical neuroncentric model of Alzheimer's disease pathophysiology.

Ketamine's negating of early developmental stress consequences in Alzheimer's disease

Recent work on major depressive disorder (MDD) [28] and Bipolar disorders (BD) [83] highlight the causal role of early developmental stress/trauma in increasing the risk of subsequent stress-induced MDD or BD depression. This is proposed to be powerfully determined by the effects of raised cortisol on astrocyte mitochondrial function. Low level cortisol enhances astrocyte mitochondrial function by activating the glucocorticoid receptor (GR)-α, possibly located on the astrocyte mitochondrial outer membrane [84], including by increasing ATP production. In contrast, stress levels of cortisol increase astrocyte reactivity [85] leading to the engulfment and destruction of neighboring synapses [86]. Consequently, stress-level cortisol can induce many of the astrocyte-driven changes seen in both Alzheimer's disease [87] and depression, namely increased BBBp, decreased glymphatic system, EAATs and lactate provision to neurons as well as suppressing synaptic plasticity and increasing synapse elimination [88]. Stress levels of cortisol also increase astrocyte amyloid precursor protein (APP) and beta-amyloid cleaving enzyme (BACE1) to increase amyloid-β production and release, which is aided by a stress/cortisol-driven decrease in the amyloid-β degrading proteases [89].

Heightened levels of stress/cortisol increase astrocyte reactivity, at least partly via the induction of an NF-κB p65/p50 dimer composition [90], which decreases cellular melatonin production, as shown in other human cell types [26]. Such putative

suppressed melatonin production and release in astrocytes would prevent local melatonin's inhibition of p-tau [91]. Increased amyloid-β and p-tau may therefore be downstream consequences arising from stress-induced increase in astrocyte reactivity and associated suppression of astrocyte mitochondrial function, leading to decreased lactate availability in neurons and associated increases in neuronal amyloid-β and p-tau [64,92,93]. Ketamine's efficacy in mood disorders may therefore be partly mediated by its capacity to negate the consequences of developmental stress/trauma on astrocyte mitochondrial function that are proposed to prime astrocytes to subsequent stress-driven changes that alter mood and cognition. Stress/heightened cortisol effects on astrocyte mitochondria can be both direct via the mitochondrial GR-α [84] and indirect via nuclear transcription and epigenetic processes [28] (see figure 1), including the release of high-mobility group box (HMGB)1 from the nucleus, which can translocate to, and modulate, mitochondria [94], as well as being released to act as an 'alarmin' the activates toll-like receptor (TLR)4 to induce NF-κB p65/p50, BACE1 and amyloid-β production [95].

Interestingly, a growing body of data highlights the association of early developmental stress/trauma with increased risk of subsequent Alzheimer's disease and wider forms of dementia [96,97]. This was first indicated in rodents where developmental stressors increased amyloid-β levels in adulthood [98]. Such data indicate pathoetiology overlaps of depression and Alzheimer's disease mediated by cortisol/GR-α modulation of astrocyte mitochondrial function. Heightened cortisol/GR-α activation increases astrocyte reactivity, thereby increasing the NF-κB p65/p50 dimer composition, which in an array of diverse human cell types decreases melatonergic pathway induction [26]. As GR-α activation also increases tryptophan 2,3-dioxygenase (TDO) [99] to decrease tryptophan availability for the tryptophan-melatonin pathway, enhanced GR-α activation may contribute to an attenuated efficacy of ketamine to modulate depression/agitation and wider pathophysiological alterations in MCI/Alzheimer's disease. This is also clearly relevant to data showing the positive association of stress and depression, especially late-life depression [100], with increased amyloid-β and p-tau [101] in the course of increasing MCI/dementia risk [102]. An 'astrocyte-centric metabolic collapse" [103], including decreased lactate provision to neurons, is proposed to be a major driver/initiator of neuronal amyloid-β and p-tau [103]. Amyloid-β and p-

tau, like glymphatic system dysfunction, may be seen as downstream consequences arising from alterations in astrocyte mitochondrial function. See figure 2.

Linking wider MCI/Alzheimer's diease pathophysiology

Figure 2 and associated text above highlight the role of developmental stress interacting with subsequent stress in MCI/Alzheimer's disease pathophysiology. Other factors linked to MCI/Alzheimer's disease susceptibility, including ApoE4 genetic susceptibility, may also be modeled as mediating effects via such core processes, including via ApoE4 significantly upregulating astrocyte melatonin production, as indicated in the C6 glioma cell line [22]. Although requiring investigation in human primary astrocytes, ApoE4 may therefore upregulate astrocyte melatonin production and efflux. Consequently, ApoE4 carriers may have had a lifetime of enhanced astrocyte melatonin production in the course of dampening CNS oxidative stress and inflammation. Factors suppressing the tryptophan-melatonin pathway, such as T2DM and hyperglycemia-associated methylglyoxal, which binds tryptophan via protein-protein interactions [76] may then leave ApoE4 carriers more vulnerable to oxidative/inflammatory challenges under conditions of melatonergic pathway suppression. This urgently requires clarification in future research.

MCI/Alzheimer's disease is also associated with suppressed parasympathetic nervous system activity, an important aspect of which is acetylcholine (ACh) release by the vagal nerve to the melatonin-inducing alpha 7 nicotinic acetylcholine receptor (α7nAChR) [104] that acts to suppress immune cell inflammatory activity [105,106]. This suggests that ketamine's induction of melatonin contributes to vagal dampening of systemic inflammatory activity. As shown in the gut in preclinical [107] and clinical studies [108], vagal activation can only dampen local inflammatory activity if the local melatonergic pathway is increased. One route whereby that can be achieved is via α7nAChR activation increasing specialized pro-resolving mediators (SPMs), which shift NF-κB from a pro-inflammatory p65/p50 to an inflammation resolution inducing, cRel/p50 [109], to increase local melatonin [26]. This may also be achieved by the systemic effects of ketamine that upregulate local melatonin production [23]. Methylglyoxal, by binding and suppressing tryptophan [76], therefore attenuates the capacity of vagal stimulation (and ketamine systemically) to upregulate local melatonin

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and inflammation resolution. Overall, vagal suppression in MCI/Alzheimer's may be intimately intertwined with mitochondrial melatonergic pathway regulation.

The CNS and systemic opioidergic systems are significantly changed in MCI/Alzheimer's disease patients and preclinical models, with a general increase in dynorphin and κ-opioid receptor activation coupled to a decrease in β-endorphin and μ-opioid receptor activation [110,111]. Ketamine induced melatonin increases pituitary β-endorphin [112], as does ketamine via its upregulation of pro-opioimelanocortin (POMC), the immediate precursor of β-endorphin [56]. Enhanced β-endorphin and μ-opioid receptor activation in the hippocampus, amygdala and N.Acc/VTA increase cognition, affect and motivation respectively, including when previously suppressed by cortisol at the GR-α [113]. These authors show cortisol at the the GR-α in the central amygdala (CeA) to induce local CRH to upregulate dynorphin/κ-opioid receptor activation, with similar effects occurring at other CNS sites [113]. Ketamine induced melatonin may modulate this via melatonin contributing to oxytocin upregulation [114]. Oxytocin acts on CeA astrocytes to suppress cortisol/GR-α induction of CRH/dynorphin/κ-opioid receptor activation via effects on astrocyte oxytocin receptors [113]. Oxytocin neuron activation in the hypothalamic paraventricular nucleus (PVN) also leads to its release in dense core vesicles that suppress PVN CRH induction and therefore the initiation of the HPA axis, consequently contributing to decreasing local cortisol production by 11β-hydroxysteroid dehydrogenase 1 (11β-HSD1) [115,116]. Oxytocin also positively allosterically modulates the μ-opioid receptor [117] and transactivates the classical BDNF receptor, TrkB [118], with ketamine also either directly activating or positively allosterically modulating TrkB [119]. By acting on mitochondria, and therefore core aspects of astrocyte and systemic cell function, ketamine is therefore proposed to have diverse downstream effects that inhibit pathophysiological changes in MCI/Alzheimer's disease.

More detailed proposed effects of ketamine on MCI/Alzheimer's pathophysiology are shown in figure 3.

Psychedelic antidepressant efficacy has been proposed to overlap with that of ketamine by modulating astrocyte mitochondrial function [83]. The potential of psychedelics in the regulation of MCI/Alzheimer's disease pathophysiology is looked at next.

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PSYCHEDELICS AND ALZHEIMER'S DISEASE

A wide array of psychedelics, including psilocybin/psilocin, lysergic acid diethylamide (LSD), mescaline, and N,N-dimethyltryptamine (DMT) have shown some efficacy as fast-acting antidepressants [83,120]. Psychedelic efficacy is typically modeled as being mediated via the serotonin (5-HT)2A receptor on neurons, especially on Layer V mPFC pyramidal neuronal dendrites [121]. Psychedelics can also activate the sigma-1-receptor at mitochondria associated membranes (MAMs) at the interface of the endoplasmic reticulum and mitochondrial reticulum [122]. As the 5-HT2Ar is dramatically increased in reactive astrocytes [123], recent work has proposed that psychedelics act on the plasma membrane 5-HT2Ar of reactive astrocytes with their common amphiphilic/lipophilic features [124] also allowing entry not only into cells but also to directly modulate mitochondria Ca^{2+} entry by acting on the sigma-1-receptor at MAMs [83]. Like ketamine, such impacts on mitochondrial ionic regulation and function have longer-term consequences proposed to be mediated by diverse epigenetic processes [120]. The antidepressant efficacy of psychedelics may therefore parallel that of ketamine by optimizing astrocyte mitochondrial function via ionic regulation, arising from a low level increase in Ca^{2+} entry into mitochondria. This is supported by preclinical data in the chronic stress model, where the efficacy of psilocybin or ketamine is mediated via astrocytes and optimized mitochondrial function, leading to enhanced lactate provision to neurons [125], thereby decreasing neuronal amyloid-β and p-tau[103]. Consequently, psychedelics can have beneficial effects in MCI/Alzheimer's disease core processes, as a growing body of data indicate [122,126], including by increasing neurogenesis and cognition [127].

As with ketamine, the antidepressant efficacy of psychedelics has been modeled via diverse processes. As well as serotonergic agonism and sigma-1-receptor activation, psychedelic efficacy has been proposed to involve a glutamate surge and monoamine release, as well as the upregulation of neuroplasticity, corticolimbic function, coupled to a maintaining effect via epigenetic processes [128]. The wider ranging effects of psychedelics on CNS function and disorders is highlighted by the efficacy of psilocybin/psilocin on traumatic brain injury in rodents, where it restores behavior and decreases microglia density and activity [129]. Given the positive impacts of psychedelics on cognition/long term potentiation [130], recent work has proposed their

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utilization for many aging-associated inflammatory conditions, including neurodegenerative disorders [131].

White matter abnormalities are common across neurodegenerative and neuropsychiatric conditions [83]. Glymphatic system dysregulation correlates with regional white matter hyperintensities as well as plasma amyloid-β burden in Alzheimer's disease [62], suggesting that the beneficial effect of psychedelics (and ketamine) on white matter remyelination [132] is another aspect of their overlapping efficacy in depression and MCI/Alzheimer's disease. The beneficial effects of ketamine and psychedelics on white matter damage are proposed to be mediated via increased release of astrocyte melatonin and humanin, which shift M1-like pro-inflammatory microglia that drive demyelination [29,133], to a remyelination associated M2-like microglia phenotype. Melatonin and humanin may also directly act on oligodendrocytes to decrease demyelination and increase remyelination [29], allowing ketamine and psychedelics to act on astrocytes at the nodes of Ranvier to attenuate/reverse the white matter damage evident in both MCI/Alzheimer's disease [62] and depression [134]. This may be especially important in MCI/early Alzheimer's disease given that white matter loss is proposed to precede gray matter loss in MCI/Alzheimer's disease [135].

The positive allosteric modulation of TrkB also significantly overlaps psychedelic and ketamine effects [136]. These authors proposed that the antidepressant effects of psychedelics, like ketamine, are mediated via the positive allosteric modulation of TrkB and its activation by BDNF [136]. The relevance of TrkB on the plasma membrane, vs mitochondrial membrane, will be important to clarify, including as to the relevance of TrkB site to the efficacy of psychedelics and ketamine in the modulation of mood and neurodegenerative conditions. As the immediate precursor of melatonin, N-acetylserotonin (NAS), is a BDNF mimic via its activation of TrkB [53] and variations in the NAS/melatonin are a typically unmeasured aspect of melatonin release [137], the induction of NAS by psychedelics (and ketamine) will be important to clarify. Preclinical data shows NAS to increase BDNF in the hippocampus [54], suggesting that the availability of the melatonergic pathway and the NAS/melatonin ratio may be relevant modulators of BDNF induction and TrkB activation. Unlike ketamine, psychedelics do not increase cAMP/PKA to initiate the melatonergic pathway. However, psychedelics do modulate STAT3 [138] and NF-κB [139,140], including

inhibiting the proinflammatory dimer composition of NF-κB, suggesting possible regulation of the mitochondrial melatonergic pathway via STAT3-NF-κB interactions [26]. The capacity of NAS to activate TrkB indicates that the availability and induction of the mitochondrial melatonergic pathway may be a relevant aspect of psychedelic and ketamine efficacy in CNS conditions and requires investigation in future studies.

As classical psychedelics share structural similarity to tryptophan metabolites, psychedelics can activate the aryl hydrocarbon receptor (AhR) [139]. Ketamine does not seem to activate the AhR, but rather ketamine is biotransformed by the hepatic AhR via its regulation by glucuronidation [141]. The AhR has complex effects that can be ligand, cell and site dependent [142]. AhR activation, including by psychedelics increases cytochrome P450 (CYP)1A1, CYP1B1 and CYP1A2, which can hydroxylate melatonin, to dramatically decrease its effects, or *O*-demethylate melatonin to its immediate precursor, NAS [55,143,144]. The association of the AhR with psychedelic effects may therefore have significant impacts on the NAS/melatonin ratio, with consequences for TrkB activation by NAS as well as NAS induction of BDNF [54]. This will be important to clarify as the AhR has been intimately associated with aging and neurodegenerative processes/conditions [145], including Alzheimer's disease [146,147]. Interestingly, AhR activation increase astrocyte ApoE secretion [148], with ApoE, especially ApoE4, secretion generally detrimental in Alzheimer's disease [149]. As melatonin has complex, generally negative reciprocal interactions with the AhR [150,151,152], the suppression of astrocyte and other sources of melatonin may therefore contribute to AhR induction of ApoE release in MCI/Alzheimer's disease. Whether psychedelics, via AhR activation, can contribute to MCI/Alzheimer's disease pathophysiology including by increasing ApoE secretion will be interesting to clarify in future research. This may indicate that the capacity of ApoE4 to upregulate astrocyte melatonin secretion only becomes problematic in older age when the astrocyte tryptophan-melatonin pathway is suppressed e.g. during T2DM/metabolic syndrome associated increase in methylglyoxal, thereby allowing the astrocyte AhR to become disinhibited re ApoE4 secretion but without concurrent increases in NAS/BDNF and TrkB activation. This is supported by data showing T2DM to interact with ApoE4 to increase cognitive loss and Alzheimer's disease risk [153,154,155,156]. Whether this is mediated by T2DM driven hyperglycemia that increases methylglyoxal's protein-protein interactions with tryptophan to suppress the tryptophan-melatonin pathway [76]

will be important to clarify. This may be another route whereby ApoE4 leads to a lifetime of increased dependence on astrocyte melatonin to achieve local inflammation/oxidant resolution, with the suppression of the tryptophan-melatonin pathway more markedly influencing entrained physiological processes in ApoE4 carriers, thereby increasing Alzheimer's disease risk. This will be important to clarify in future research.

Like the GR-α, the AhR can be expressed in the cytoplasm and on the mitochondrial membrane, where it regulate the voltage dependent anion channel (VDAC)1 to modulate Ca^{2+} influx into mitochondria [157]. The capacity of psilocybin/psilocin to induce BDNF requires AhR activation [139], possibly via AhR/NAS/BDNF/TrkB activation. The AhR also regulates MAMs by modulating key transcriptional targets such as transglutaminase 2 (TGM2), which dictates the physical and functional apposition/alignment of endoplasmic reticulum-mitochondria contact sites (MAMs), as well as regulating cellular redox balance and endoplasmic reticulum stress pathways [158,159]. The AhR can influence mitochondrial Ca^{2+} influx, at least partly via inositol 1,4,5-trisphosphate receptor (IP3R)/VDAC1/mitochondrial calcium uniporter (MCU) [160,161], suggesting that psychedelics, like ketamine [83] have wider impacts on mitochondrial ionic regulation but by different routes.

Proposed psychedelics effects in MCI/Alzheimer's disease are shown in figure 4.

The distinct effects of ketamine and psychedelics on astrocyte mitochondrial function in MCI/Alzheimer's disease have a number of future research and treatment implications.

FUTURE RESEARCH IMPLICATIONS

Given that T2DM interacts with ApoE4 to increase cognitive loss and Alzheimer's disease risk [153,154,155,156], does this arise from astrocyte ApoE4 increasing melatonin release [22] leading to a lifetime increased dependence on astrocyte melatonin in ApoE4 carriers to achieve local inflammation/oxidant resolution? Is this compromised by T2DM/metabolic syndrome/hyperglycemia increasing methylglyoxal to bind with tryptophan and therefore limit the initiation of the tryptophan-melatonin pathway [76]? Would quercetin's quenching of methylglyoxal prevent/attenuate the increased risk of Alzheimer's disease by T2DM, perhaps especially in ApoE4 carriers?

Does ketamine, via increased cAMP/PKA, not only increase the melatonergic pathway but also increase cAMP/PKA-induced IL-33, especially under conditions of challenge/inflammation as in other cell types [162], to modulate astrocyte and microglia phenotypes [163] in the course of Alzheimer's disease [164]? The relevance of IL-33 in Alzheimer's disease is highlighted by preclinical data showing astrocyte IL-33 to be necessary for astrocyte AQP4 upregulation and therefore crucial to glymphatic system function and p-tau clearance [165]. As IL-33 is typically described as an 'alarmin', the dampening/resetting effects of melatonin include IL-33 downregulation, as shown in other cell types [166]. However, in the course of CNS inflammation melatonin, via the MT2 receptor, can increase IL-33 [167]. The interactions of ketamine, cAMP/PKA, melatonin and IL-33 in the MCI and Alzheimer's disease CNS require further investigation, including as arising from the proposed ketamine upregulation of the melatonergic pathway.

Given that the efficacy of ketamine and the psychedelics may be powerfully determined by their amphiphilic characteristics, future research may use these compounds as a base to develop new pharmaceuticals. To some extent this has been achieved with a novel psychedelic-like compound [168]. Clearly, the mode of efficacy of ketamine and the psychedelics e.g. re relevance of amphiphilic qualities, melatonin, humanin, mitochondrial TrkB, and tryptophan availability require experimental validation for the development of targeted and possibly more precise pharmaceuticals.

Decreased norepinephrine and locus coeruleus activity are common in Alzheimer's disease. Recent preclinical and clinical data indicate that astrocyte reactivity significantly determines the association of locus coeruleus norepinephrine-related dysfunction with raised levels of circulating tau and cognitive loss [169]. As heightened and/or prolonged GR-α activation by cortisol contributes to locus coeruleus atrophy in Alzheimer's disease [170], it will be important to determine the efficacy of ketamine and/or the psychedelics on astrocyte reactivity and locus coeruleus norepinephrine, circulating tau and GFAP in Alzheimer's disease patients.

-Do psychedelics, via AhR activation, increase the NAS/melatonin ratio, thereby allowing NAS to both activate TrkB directly [53] and/or indirectly via NAS induced BDNF [54].

Do psychedelics, via AhR activation, contribute to MCI/Alzheimer's disease pathophysiology by increasing ApoE secretion [149]. Is this only problematic when AhR activation is unable to increase NAS/BDNF and TrkB activation under conditions, such as T2DM/metabolic syndrome and increased methylglyoxal that suppresses the availability of the astrocyte tryptophan-melatonin pathway [76]? In microglia, AhR activation can increase microglia reactivity [171], although not always [172], whilst melatonin induces an M2-like microglia phenotype which may be partly dependent upon the tyrosine 239 phosphorylation of the AhR^{Tyr239}, which dampens microglia activation, including by increasing endogenous antioxidants via Nuclear factor erythroid 2-related factor 2 (Nrf2) upregulation [173]. The interactions of melatonin and the AhR seem likely to complicate psychedelic effects on astrocytes and microglia and clearly require future investigation.

Oxidant increase in Alzheimer's disease is associated with the induction and activation of a number of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX) isoforms. Suboptimal mitochondrial function induced oxidants can increase NOX [174], whilst NOX-induced oxidants can contribute to mitochondrial dysfunction [174]. NOX-1, -2 and -4 are expressed in astrocytes, with NOX-1 suppression in preclinical models prolonging the antidepressant efficacy of ketamine [175]. Whether a similar enhancement of putative protective ketamine effects in MCI and Alzheimer's disease occurs will be important to determine. Psychedelics similarly suppress NOX, with effects, as with ketamine, at least partly mediated via attenuating NF-κB p65/p50 induction [176]. Preclinical data show aging and stress levels of cortisol to increase brain NOX [177], suggesting role of NOX in both the pathoetiology and pathophysiology of MCI and Alzheimer's disease. The interactions of NOX isoforms in astrocytes and microglia with the efficacy of ketamine and the psychedelics will be important to determine in preclinical models of MCI and Alzheimer's disease as well as in clinical studies.

Does the ketamine/psychedelics influence on the gut barrier/microbiome [178,179] modulate gut-derived extracellular vesicles proposed to contribute to Alzheimer's disease pathophysiology [180]?

Although psychedelics have many overlapping effects such as 5HT2Ar agonism and many have DMT as a core structure, it is clear that they also have distinct effects both

in the brain and systemically. It will be important for future research to clarify the advantages and disadvantages of distinct psychedelic effects on Alzheimer[s disease pathophysiology and any interactions with risk factors or genetic susceptibility genes

Safety and translational implications

As the above has highlighted both prevention and combination treatments, it will be crucial for future research to address wider issues, including cognitive and behavioral effects, cardiovascular monitoring, psychiatric vulnerability, repeated exposure, drug interactions, and feasibility in cognitively impaired older adults. The proposed combination treatments therefore require extensive clinical research studies before any treatment interventions are attempted. It will also be important for future research to investigate any interactions of ketamine, psychedelics or combinatorial treatments with genetic variations in genes associated with Alzheimer's disease risk, including ApoE4 and presenelin-1 and presenelin-2. The possible utility of melatonin and/or oxytocin with ketamine or psychedelic treatment also requires extensive investigation in clinical trials.

TREATMENT IMPLICATIONS

Given the attenuated anti-depressant effects of ketamine in people with T2DM/metabolic syndrome [77] and the high incidence of T2DM/metabolic syndrome in MCI/Alzheimer's disease [181], would ketamine efficacy be enhanced by the prior utilization of quercetin to quench methylglyoxal [78], thereby increasing tryptophan availability for the tryptophan-melatonin pathway [76], which is proposed to be an important aspect of ketamine efficacy?

The investigation of the relevant pathophysiological processes in MCI and Alzheimer's disease highlighted above as well as the mode(s) of ketamine and psychedelics efficacy should provide a knowledge base for the development of novel pharmaceuticals, as indicated by the recent development of a novel psychedelic-like compound [168].

There is a growing interest in the utilization of near infra-red photobiomodulation in the treatment of diverse medical conditions, including MCI and Alzheimer's disease [182,183], given the capacity of this treatment to decrease mitochondrial oxidants and better optimize mitochondrial function [184]. As ketamine is proposed to mediate its effects by optimizing mitochondrial function in astrocytes, would there be utility in

combining ketamine treatment with photobiomodulation? Would a combination of ketamine and photobiomodulation still require an available tryptophan-melatonin pathway? Would supplementation with tryptophan and/or quercetin modulate ketamine, photobiomodulation and psychedelic efficacy, including when used in combination?

Given the associations of T2DM with Alzheimer's disease risk [185], there is a growing body of preclinical data indicating the utility of glucagon-like peptide-1 receptor (GLP-1R) agonists in the treatment and possibly prevention of Alzheimer's disease [186]. However, this is not strongly supported by clinical trials of long-established Alzheimer's disease [186]. The role of GLP-1R agonists in the prevention of Alzheimer's disease, including deterioration from MCI, may prove more useful [187], although this is not indicated by all data [188]. The capacity of GLP1-R agonists to increase cAMP [189] and therefore the AANAT initiation of the melatonergic pathway [25], may be important to determine, especially in astrocytes. GLP-1R agonist effects in astrocytes decrease astrocyte reactivity [190] and can optimize mitochondrial function, including increasing OXPHOS and PGC-1α, as shown across diverse cell types [191,192], indicating plausible beneficial effects in preventing the emergence of MCI and Alzheimer's disease.

A number of other repurposed medications can suppress stress/cortisol induced changes in astrocyte reactivity, including sildenafil (viagra) [193,194]. Although classically defined as a phosphodiesterase (PDE)5 inhibitor, leading to increased cyclic guanosine monophosphate (cGMP), sildenafil can also indirectly increase cAMP/PKA [195,196] and increase TrkB activation by BDNF [194,197] as well as optimize mitochondrial function [198], including to amyloid-β challenge [199], improve mood preclinically [200] increase oxytocin preclinically [201] and suppress NF-κB p65/p50 [202], indicating some relevant overlaps of sildenafil with ketamine/psychedelics. Preclinical and in vitro data indicate some utility of sildenafil in Alzheimer's disease, primarily as indicated by decreased amyloid-β and p-tau and associated toxicity [199,203]. Some clinical data is highly suggestive of utility [195,204] but likely to complicated by other variables [205]. However, given the overlapping effects on Alzheimer's disease pathophysiology, the interactions of sildenafil and ketamine/psychedelics will be interesting to explore preclinically and clinically.

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CONCLUSIONS

There is a growing dissatisfaction at classical conceptualizations of MCI/Alzheimer's disease pathoetiology and pathophysiology, given the over-emphasis on the importance of amyloid-β and p-tau. As indicated above, these classical pathological proteins may be relatively minor downstream aspects of MCI/Alzheimer's disease pathophysiology, which is proposed to be centred on astrocyte mitochondrial function. This is parsimonious with the diverse pathophysiological processes regulated by astrocytes and which emerge under conditions of astrocyte reactivity and suboptimal mitochondrial function, including increased BBBp and synapse elimination, coupled with decreased glymphatic system function, EAATs and lactate provision to neurons. The suppression of neuronal lactate availability is a major driver of neuronal amyloid-β and p-tau upregulation, further emphasizing the primacy of astrocyte metabolic function in MCI/Alzheimer's disease pathophysiology. The current article has highlighted how developmental stressors/trauma, via raised cortisol suppression of astrocyte mitochondrial function, can prime not only depression susceptibility but MCI/Alzheimer's disease many decades later. The many neurotransmitter alterations in MCI/Alzheimer's disease, including norepinephrine and acetylcholine are proposed to arise from astrocyte dysfunction, which is supported by a growing body of data. It is upon these core astrocyte mitochondrial processes that ketamine and the psychedelics are proposed to act. This is achieved by diverse processes, with ketamine proposed to be acting via the inner mitochondrial membrane NMDAr and the psychedelics acting via diverse processes, including the AhR, sigma-1-receptor and 5-HT2AR, whilst both ketamine and psychedelics act as positive allosteric modulators of the classical BDNF (and NAS) receptor, TrkB. It will be important for future research to clarify these proposed effects of ketamine and the psychedelics, including as to the relevance of the tryptophan-melatonin and mitochondrial melatonergic pathways. Ketamine and the psychedelics highlight novel pathophysiological targets for MCI/Alzheimer's disease treatment and perhaps prevention, for which investigation of the presence and regulation of the tryptophan-melatonin pathway in astrocytes would be an important starting point.

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FIGURES WITH LEGENDS

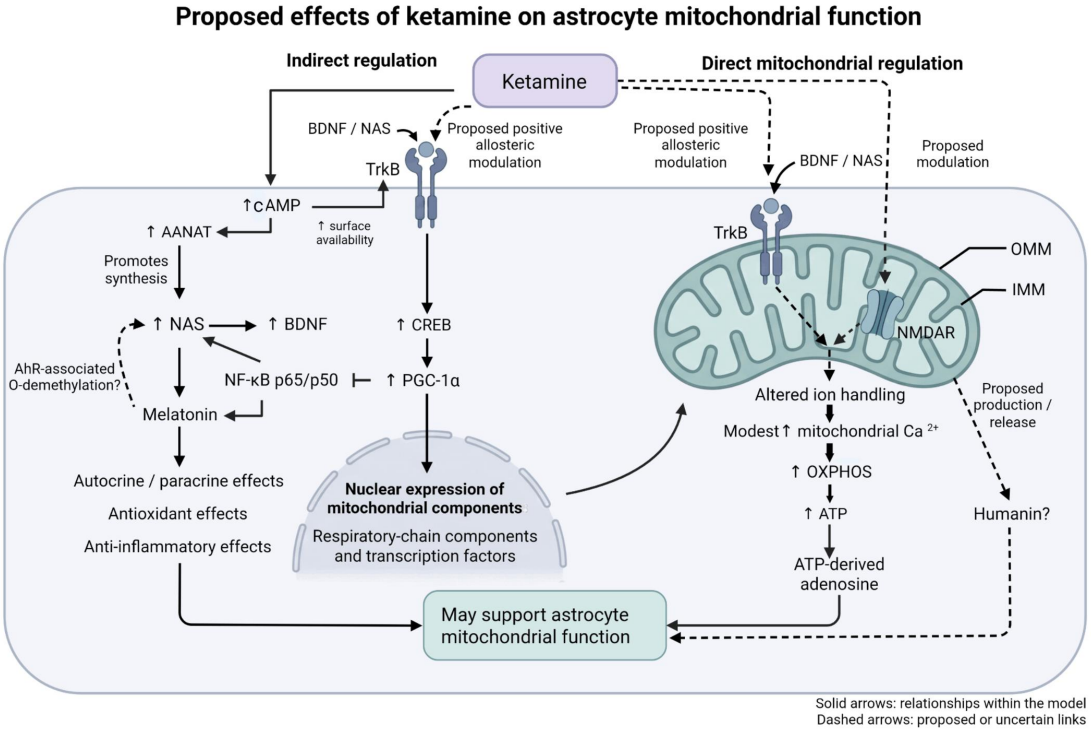

Figure 1. Proposed direct and indirect effects of ketamine on astrocyte mitochondrial function. Direct mitochondrial pathways involve the proposed modulation of inner mitochondrial membrane NMDAr and positive allosteric modulation of outer mitochondrial membrane TrkB, which is activated by BDNF and NAS. These interactions can alter mitochondrial ion handling that culminate in a modest rise in mitochondrial Ca^{2+}, which enhances OXPHOS and ATP production. ATP-derived adenosine may further support mitochondrial function; a contribution from increased humanin production and release remains hypothetical. Indirect pathways link increased cAMP to AANAT upregulation and greater TrkB availability at the plasma membrane. TrkB–CREB–PGC-1α signaling may enhance the nuclear expression of mitochondrial components and transcription factors. In parallel, activation of the melatonergic pathway may increase NAS and melatonin availability. NAS may reinforce TrkB signaling through direct receptor activation and BDNF induction, while AhR-regulated *O*-demethylation of melatonin provides a potential additional source of NAS. PGC-1α-mediated suppression of NF-κB p65/p50 may relieve inhibition of the melatonergic pathway. Melatonin is depicted as an autocrine and paracrine mediator of antioxidant, anti-inflammatory, and mitochondrial effects.

Question marks indicate proposed links requiring experimental validation in astrocytes. **Abbreviations**: AANAT, aralkylamine N-acetyltransferase; AhR, aryl hydrocarbon 50receptor; ATP, adenosine triphosphate; BDNF, brain-derived neurotrophic factor; Ca^{2+}, calcium ions; cAMP, cyclic adenosine monophosphate; CREB, cAMP response element-binding protein; NAS, N-acetylserotonin; NF-κB, nuclear factor kappa B; NMDAr, N-methyl-D-aspartate receptor; OXPHOS, oxidative phosphorylation; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1-alpha; TrkB, tropomyosin receptor kinase B.

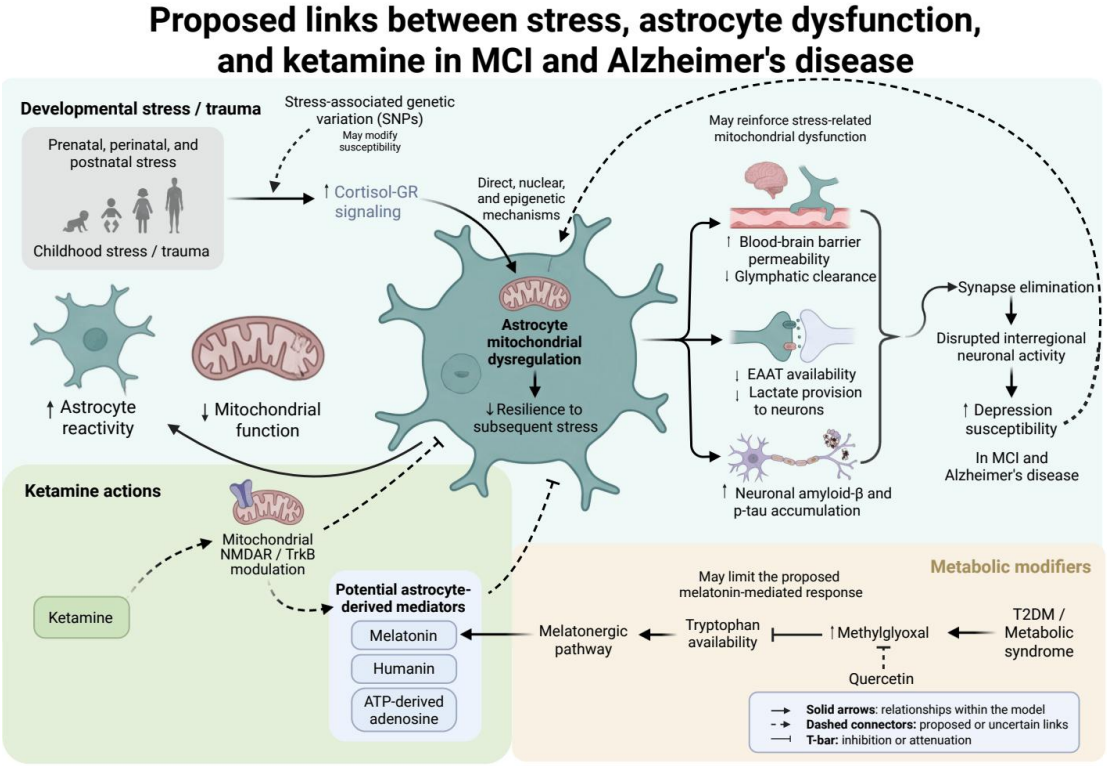

Figure 2. Proposed links between developmental stress, astrocyte mitochondrial dysfunction, and ketamine effects in MCI and Alzheimer's disease. The model links developmental stress or trauma, potentially modified by stress-associated SNPs, to increased cortisol–GR signaling and astrocyte mitochondrial dysregulation through direct, nuclear, and epigenetic mechanisms. The reduced mitochondrial resilience to subsequent stressors can increase astrocyte reactivity and BBBp, promote neuronal amyloid-β and p-tau accumulation, and decrease EAAT availability, lactate provision to neurons, and glymphatic function. These alterations may contribute to synapse elimination, disrupted inter-regional neuronal activity, and increased susceptibility to

depression, which may further reinforce stress-related mitochondrial dysfunction. Ketamine is proposed to counteract these processes through mitochondrial NMDAr and TrkB regulation, potentially involving astrocyte-derived melatonin, humanin, and ATP-derived adenosine. The question mark denotes the unconfirmed contribution of these mediators to ketamine's effects in astrocytes. T2DM or metabolic syndrome may increase methylglyoxal, thereby reducing tryptophan availability for the melatonergic pathway and potentially attenuating the proposed response to ketamine. Quercetin can quench methylglyoxal, thereby preserving tryptophan availability, although this requires experimental investigation in astrocytes. These potential effects on disease progression and the proposed ketamine–quercetin combination require experimental and clinical investigation. **Abbreviations**: ATP, adenosine triphosphate; BBBp, blood–brain barrier permeability; EAATs, excitatory amino acid transporters; GR, glucocorticoid receptor; MCI, mild cognitive impairment; NMDAr, N-methyl-D-aspartate receptor; p-tau, hyperphosphorylated tau; SNPs, single nucleotide polymorphisms; T2DM, type 2 diabetes mellitus; TrkB, tropomyosin receptor kinase B.

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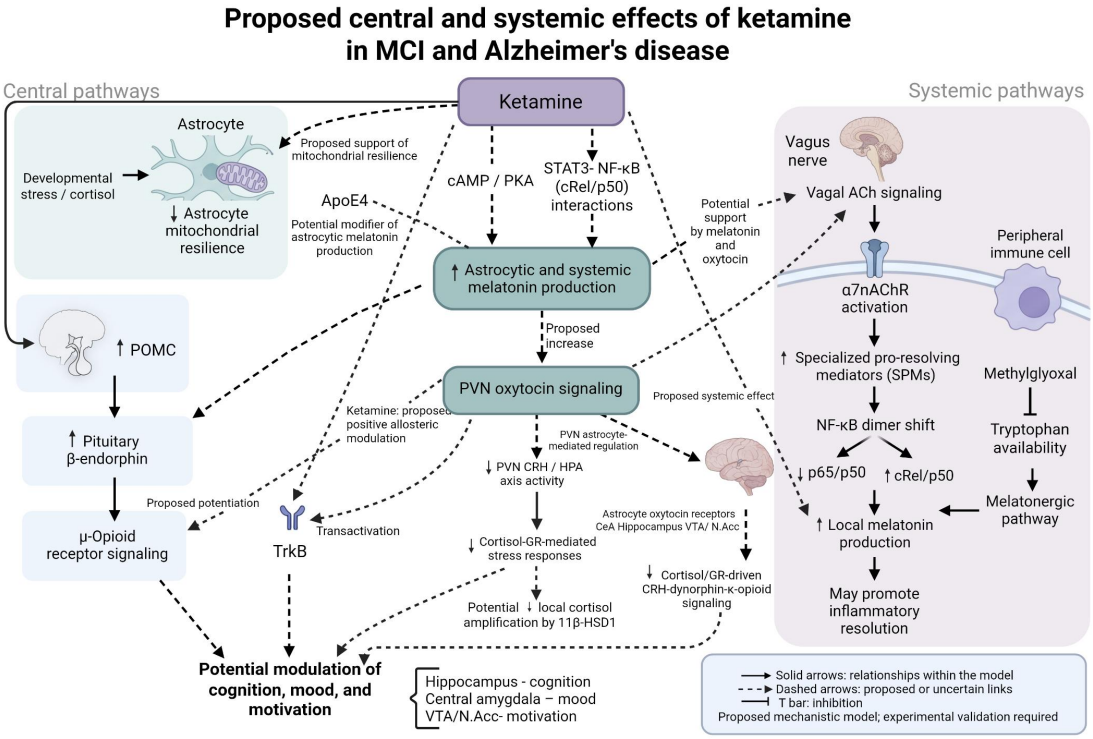

Figure 3. Proposed central and systemic effects of ketamine in MCI and Alzheimer's disease. Ketamine is proposed to counteract developmental stress/cortisol-associated loss of astrocyte mitochondrial resilience and enhance astrocytic and systemic melatonin production through cAMP/PKA signaling and STAT3–NF-κB (cRel/p50) interactions. ApoE4 is included as a potential modifier of astrocytic melatonin production. Ketamine-associated POMC induction and melatonin are linked to increased pituitary β-endorphin and μ-opioid receptor activation. Astrocyte and systemic melatonin can increase hypothalamic oxytocin. Oxytocin may reinforce μ-opioid signaling and transactivate TrkB, while ketamine can positively allosterically modulate TrkB. In the PVN, oxytocin is proposed to suppress CRH and HPA axis activity, potentially reducing GR-mediated stress responses and local cortisol amplification by 11β-HSD1. Oxytocin signaling at astrocyte receptors in the CeA, Hippocampus, and VTA/N.Acc is proposed to attenuate cortisol/GR–CRH–dynorphin/κ-opioid pathways, with potential effects on mood, cognition, and motivation, respectively. Systemically, melatonin and oxytocin can support vagal ACh–α7nAChR signaling and SPM-associated shifts in NF-κB from p65/p50 to cRel/p50, thereby promoting local melatonin production and inflammatory resolution. Ketamine's proposed systemic effects converge on local melatonin production, which methylglyoxal may impair by limiting tryptophan availability. **Abbreviations**: 11β-

HSD1, 11β-hydroxysteroid dehydrogenase 1; α7nAChR, alpha 7 nicotinic acetylcholine receptor; ACh, acetylcholine; ApoE4, apolipoprotein E4; cAMP, cyclic adenosine monophosphate; CeA, central amygdala; CRH, corticotropin-releasing hormone; GR, glucocorticoid receptor; Hippo, hippocampus; HPA, hypothalamic–pituitary–adrenal; MCI, mild cognitive impairment; N.Acc, nucleus accumbens; NF-κB, nuclear factor kappa B; PKA, protein kinase A; POMC, proopiomelanocortin; PVN, hypothalamic paraventricular nucleus; SPMs, specialized pro-resolving mediators; STAT3, signal transducer and activator of transcription 3; TrkB, tropomyosin receptor kinase B; VTA, ventral tegmental area.

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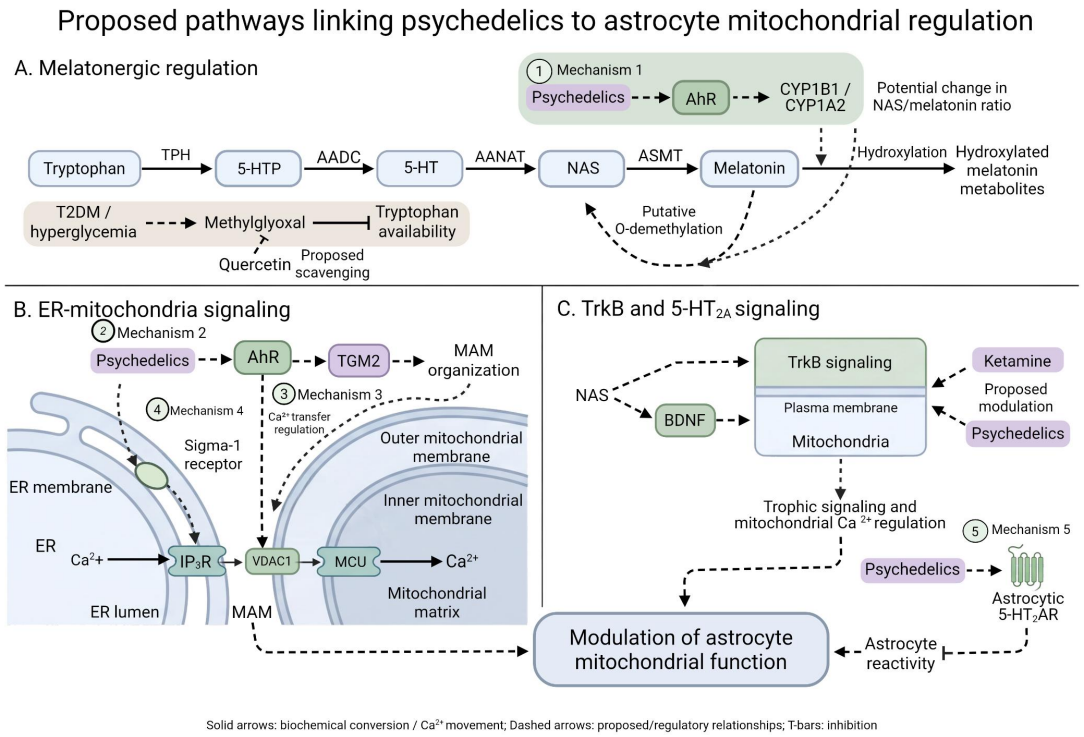

Figure 4. Proposed pathways linking psychedelics to astrocyte mitochondrial regulation. The tryptophan–melatonin pathway and TrkB-related components are shown in Section A, and their regulation by AhR-associated processes, and psychedelics and selected receptor targets. Quercetin is shown as a potential methylglyoxal scavenger that may preserve tryptophan availability. Across Sections A, B and C numbered boxes identify five proposed mechanisms. Section A highlights (1) AhR regulated metabolism of melatonin by cytochrome P450 enzymes, including hydroxylation and putative *O*-demethylation to NAS, potentially altering the NAS/melatonin ratio. The ? indicates the need to investigate the AhR regulation of the NAS/melatonin ratio in astrocytes and neurons. In Section B, ER-mitochondrial signaling: (2) AhR-associated regulation of TGM2 and MAM formation; (3) AhR-associated modulation of IP3R–VDAC1–MCU-mediated Ca^{2+} transfer between the endoplasmic reticulum and mitochondria; (4) sigma-1 receptor-mediated regulation of Ca^{2+} signaling at MAMs. In Section C, mechanism (5) shows astrocytic 5-HT2AR activation, which inhibits astrocyte reactivity and mitochondrial dysfunction. Psychedelics activation of the AhR to increase NAS can activate TrkB directly and indirectly through BDNF induction, linking plasma membrane and mitochondrial TrkB signaling to trophic responses and mitochondrial Ca^{2+} regulation. Ketamine and psychedelics are depicted as converging on TrkB signaling. The contribution and

direction of these effects may vary across different psychedelics and biological contexts and requires experimental investigation. **Abbreviations**: 14-3-3η, 14- 3-3 protein eta; 14-3-3ζ, 14-3-3 protein zeta; 5-HT, 5-hydroxytryptamine (serotonin); 545-HT2AR, 5-hydroxytryptamine 2A receptor; 5-HTP, 5-hydroxytryptophan; AADC, aromatic L-amino acid decarboxylase; AANAT, aralkylamine N-acetyltransferase; acetyl-CoA, acetyl coenzyme A; AhR, aryl hydrocarbon receptor; ASMT, N- acetylserotonin O-methyltransferase; BDNF, brain-derived neurotrophic factor; Ca^{2+}, calcium ions; CYP1A2, cytochrome P450 1A2; CYP1B1, cytochrome P450 1B1; IP3R, inositol 1,4,5-trisphosphate receptor; MAMs, mitochondria-associated membranes; MCU, mitochondrial calcium uniporter; NAS, N-acetylserotonin; T2DM, type 2 diabetes mellitus; TGM2, transglutaminase 2; TPH, tryptophan hydroxylase; TrkB, tropomyosin receptor kinase B; VDAC1, voltage-dependent anion channel 1.

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