Psychedelics and Response Duration

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INTRODUCTION

Over the last century, diseases of despair (DoD) have become alarmingly prevalent. Suicide, addiction, and related illnesses represent some of the most significant contributors to increasing morbidity and mortality worldwide [1]. Indeed, depressive symptoms form a core amalgamation across these tragedies. Unfortunately, conventional (mostly monoaminergic) treatments have historically failed to provide relief for many, with delayed responses, high rates of relapse, and undesirable side effects [2].

The discovery of ketamine's rapid antidepressant effects (even in treatment-resistant patients) represented a paradigm shift in both our therapeutic and mechanistic understanding of DoDs [3,4]. Likewise, the recent revival of psychedelic-assisted psychotherapy with psilocybin, lysergic acid diethylamide (LSD), ayahuasca, N,N-Dimethyltryptamine (DMT), and others holds significant potential. Though far more validation is needed, the rapid onset of action and large effect sizes seen with these compounds represents arguably the most promising advance in mental healthcare in over a half-century.

Common to all the rapid-acting antidepressants appears to be variable effects on glutamatergic modulation, which in turn enhances "neuroplasticity"-broadly interpreted to be a prominent underpinning of most depressive phenotypes and treatments [5].

Unlike ketamine's short duration of response, serotonergic hallucinogens (SHs) appear to produce positive effects lasting months (and possibly years) after only a few doses [6–10]. Adjunctive psychotherapy with SHs would seem a likely answer—albeit incomplete. Though data regarding ketamine-assisted psychotherapy (KAP) is sparse, unlike with SHs, it appears that repeated ketamine infusions do not enhance the antidepressant or anxiolytic effects of KAP at long-term follow-up [11].

As follows, understanding the neurobiological underpinnings which differentiate the response duration of these psychedelic therapies holds significant potential for patients and practitioners alike. Herein, we will outline some of the most prominent mechanisms of action for these compounds that may explain this difference, highlighting areas for future research, with a specific focus on the roles of inflammation, epigenetics, opioid receptor mechanics, and neuroplasticity.

GLUTAMATE, NEUROPLASTICITY, AND CONNECTIVITY

Ketamine and SHs espouse several similarities regarding their immediate mechanisms of action. Ketamine, psilocybin, and LSD appear to similarly enhance spontaneous signal complexity ("entropy") directly following administration [12]. Both classical and dissociative psychedelics appear to temporarily reduce functional connectivity within the default mode network (DMN) and increase interconnectivity with other resting-state networks related to depression [13–16]. Measures of signal transmission and connectivity are thought to reflect underlying neurochemical homeostasis, particularly with regards to glutamate—the brain's predominant excitatory neurotransmitter [17].

In that regard, both ketamine and SHs trigger a rapid increase in excitatory

signaling ("glutamate surge") in layer V pyramidal neurons throughout the different cortico-limbic regions [18,19]. This is widely believed to upregulate the protein synthesis necessary for neuro-synaptogenesis via increased expression of brain-derived neurotrophic factor (BDNF) and its downstream effector molecules (TrKB and mechanistic target of rapamycin complex 1 (mTORC1)—a specialized protein complex that powerfully regulates cellular proliferation, inflammation, and energy metabolism) [2,20].

SHs accomplish this process via direct pyramidal serotonin (5HT)-2A receptor stimulation, whereas ketamine is suggested to have more pleiotropic and indirect effects [2,21]. Briefly, ketamine inhibits NMDA receptors on neighboring inhibitory interneurons, increasing glutamate release within relevant synapses. Following disinhibition, glutamate is shunted towards neighboring AMPA receptors—the expression of which ketamine also upregulates. This is classically known as the "NMDA to AMPA throughput" model, which is thought to facilitate calcium influx into the dendritic compartment, modulating excitability and plasticity [22].

Importantly, numerous other mechanisms have been proposed for the immediate antidepressant effects of ketamine (and its metabolites), many of which are independent of NMDA receptor inhibition [2]. Notwithstanding, compelling preclinical and human evidence suggests that AMPA-receptor-dependent increases in BDNF-TrkB-mTORC1 signaling are required for the behavioral, antidepressant, and neuroplastic effects seen with ketamine and most SHs [2,19,23–25]. Notably, differential dendritic excitation patterns based on the location of 5-HT vs. NMDA/AMPA receptors along synapses have been suggested to contribute to differences in neuroplasticity realized by these compounds (see the following review for a more detailed explanation) [18].

In vitro, SHs (particularly LSD) appear to more potently upregulate BDNF-TrkB-mTORC1 signaling than ketamine [26]. However, blockade of either TrkB or mTORC1 appears to completely prevent the neuroplastic effects of both ketamine and SHs [26], suggesting a limiting reagent in this pathway that is independent of initial stimulus potency. Moreover, enhanced neuroplastic signaling realized through repeated acute-phase administration of ketamine still confers relapse in the vast majority of patients within the first month following their final infusion [27]. As follows, evidence for the correlation between increased BDNF levels and treatment response appears somewhat inconsistent across studies with ketamine and SHs [19]. Thus, we suggest that alternative mechanisms may also contribute significantly to discrepancies in response duration.

MTORC1 SIGNALING

Rapamycin is an mTORC1 inhibitor that confers potent immunosuppressive and anti-aging properties [28]. In line with aforementioned *in vitro* studies, when administered directly into the prefrontal cortex (PFC) of rodents, rapamycin appears to block the immediate neuroplastic and antidepressant effects of ketamine completely [29,30]. Indeed, it is known that low-physiologic levels of neuroinflammation are necessary to promote synaptic plasticity and neurotransmission [31]. Conversely, despite being quite brain-penetrant, systemically administered rapamycin has failed to block antidepressant effects of ketamine in rodents [32]. Importantly, in a recent first-in-class randomized trial, Abdallah et al. found that pre-administration with a single dose of rapamycin might

significantly prolong ketamine's antidepressant effects in humans [33]. Though these findings require further validation, they warrant attention for our purposes.

Independently, rapamycin itself has equivocal antidepressant effects [34]. However, systemic alterations in metabolic and inflammatory activity have been observed in humans and animals, lasting months after a single dose [35,36]. Mechanistically, mTORC1 acts as a rheostat, creating a "set-point" for t inflammatory and growth activity b the availability of nutrients and environmental conditions [28]. Inhibition of mTORC1 "lowers" that set point, promoting sustained reductions in both central and peripheral inflammation, improved blood-brain barrier integrity, and increased cellular autophagy [37]—a mechanism that has been proposed for many conventional antidepressants [38].

The acute antidepressant effects of ketamine have been observed through both mTORC1-dependent and (to some degree) independent mechanisms [2]. As discussed in the following section, we suggest that ketamine's acute therapeutic effects may be rapidly degraded when patients regress into a baseline state of chronic inflammation underlying their depression. Systemic administration of rapamycin may temporarily lower their inflammatory "set-point" without completely inhibiting initial neuroplastic signals. Indeed, in Abdallah et al., response rates were identical between groups at 24 hours but were more than three-fold higher in the rapamycin group at two weeks [33]. Taken together, this may explain why rapamycin-induced immunosuppression could enhance (or at least fail to inhibit) ketamine's antidepressant effects in humans.

INFLAMMATION

Peripheral and central inflammation appear to be reliable, highly correlative findings in depression, associated with aberrant glutamate signaling and compromised neuroplasticity [39]. Meta-analyses suggest that over half of depressed patients show elevations in inflammatory markers, which are reflected in the serum [40]. Moreover, nuanced, proinflammatory behaviors also occur at the single-cell level, which are just starting to be investigated in neuropsychiatric conditions [41]. It is thus likely that most (if not all) patients with depression have some degree of inflammatory aberrancy.

With few exceptions (ECT and targeted anti-inflammatory drugs), elevated baseline inflammation is associated with treatment resistance to most antidepressants [42,43]. Conversely, ketamine's inflammatory profile in depression remains elusive. Conflicting results exist when attempting to correlate treatment response (or resistance) with baseline inflammation and post-treatment suppression across trials [42,44–48]. As previously suggested, the effects of chronic inflammation may act to subvert the rapid antidepressant effects of ketamine. We further suggest that the sustained effects of SHs may be partially related to their superior efficacy in suppressing chronic inflammation—a property that ketamine lacks.

Ketamine's complex immunomodulatory characteristics are best described through research into its analgesic efficacy—where doses are comparable to those used in depression. Much like its antidepressant effects, analgesic relief appears to be short-lived, and its utility in chronic pain management remains controversial [49]. Interestingly, it appears best suited for pain types that espouse a tonic-inflammatory component (i.e., neuropathic, cancer, etc.) [49].

Unlike many neuropsychiatric conditions (where broad suppression of

chronic neuroinflammation appears to be therapeutic), full elaboration of systemic, pro-inflammatory signaling is often necessary to promote successful tissue repair in pain treatment [50]. Pain experts describe ketamine as a "homeostatic immune regulator" as opposed to a purely anti-inflammatory agent [50]. This moniker is derived from the fact that it appears to prevent exacerbation of local inflammation without interfering with broader immune signaling cascades. This unique property has been suggested to contribute to ketamine's high clinical utility in perioperative and critical care settings [49,50].

The balance between pro- and anti-inflammatory effects in this setting is believed to be largely mediated by T-helper cell populations [50]. Indeed, while ketamine and morphine both reduce T-helper cell activity in response to inflammatory stimuli, morphine favors anti-inflammatory Th2 differentiation, while ketamine promotes a relative increase in pro-inflammatory Th1 populations [51]. These findings agree with broader themes of *in vitro* ketamine research, where it appears to have little impact on cytokine expression unless administered in the presence of an inflammatory stimulus. As well, in such cases, it appears to exclusively modulate pro-inflammatory cytokine activity [50].

Conversely, SHs consistently appear to exert potent anti-inflammatory effects across many different disease models and cell lines [52–55]. 2,5-dimethoxy-4-iodoamphetamine (DOI), a synthetic derivative of mescaline, is perhaps the most-studied SH with regards to inflammation. It has been shown to profoundly suppress TNF-α mediated inflammation *ex vivo*, even at picomolar concentrations. With the exception of a few naturally occurring substances (i.e., botulinum toxin), no commercially available compound has demonstrated comparable immunosuppressive potency [55]. Likewise, due to its potent immunosuppressive capacity, DMT was recently granted orphan drug designation by the FDA for the treatment of ischemia-reperfusion injury in solid organ transplant [56] and is garnering significant attention from pharma for other neuroinflammatory conditions [57,58].

One recent clinical trial has demonstrated CRP reductions which correlate with an initial response to ayahuasca [59]. To our knowledge, no clinical trial to date has published negative results regarding cytokine changes with SHs. However, biomarker reporting in psychedelic studies is infrequent, and none have provided longitudinal tracking of inflammatory markers after SH administration. We suggest that longitudinal inflammatory monitoring and single-cell secretome analysis should be a priority in future trials with these compounds.

OPIOID RECEPTOR MECHANICS

Opioid receptor signaling has been deeply implicated in depression [60] and appears to be important for psychedelics in general. Mu-opioid activation appears to attenuate 5HT-2A downstream activity in layer V pyramidal neurons [61], a key site of action for all SHs. Conversely, LSD specifically appears to attenuate kappa-opioid receptor-mediated depressive effects in rats [62].

In obsessive-compulsive disorder, single-dose morphine and ketamine appear to have almost identical, short-lived response timelines [63]. Furthermore, nonspecific opioid receptor blockade with naloxone appears to attenuate ketamine's antidepressant (but not dissociative) effects [64,65], though these results should be interpreted carefully [66]. Indeed, dissociative effects do not appear to correlate with antidepressant response in most ketamine trials, whereas mystical experiences seem to be some of the strongest predictors of short-

term therapeutic outcomes with SHs [67]. Whether or not these observations are related to opioid signaling is a possible area of future consideration.

One relevant compound in that regard is salvinorin A. It has been reported to produce mystical/hallucinogenic effects similar to LSD, which appear to be mediated exclusively through kappa opioid receptors, with no appreciable activity at mu, 5HT-2A, or other canonical psychedelic receptors [68]. Speculation notwithstanding, the contrasting opioid signaling activity between SHs and ketamine appears to be a plausible candidate to investigate differences in both treatment duration and addictive profiles [69].

The atypical psychedelic Ibogaine also appears to be relevant to this discussion. It espouses highly pleiotropic effects but appears to act in part via 5HT-2A and receptors, possibly contributing to its applicability in addiction treatment [69].

Notably, Ibogaine also interacts with the sigma receptor family, the first of which was conceptualized as a *sigma-opioid receptor* [70]. Initially, this family was proposed to engender the psychotomimetic properties of opioids [70]. However, further investigation led not only to their independent reclassification but also uncovered profound modulation of metabolic, inflammatory, and epigenetic processes which will be discussed below.

SIGMA AND EPIGENETICS

Sigma *receptors* (sigma-1 and sigma-2) are considered highly unique. Though they possess a binding pocket and some structure-activity relationships, there are no specific endogenous ligands for either receptor and no formal transduction system [71]. Purification studies have revealed that their amino acid sequence is structurally unrelated to any known mammalian proteins, instead primarily having a shared homology with fungal proteins involved in ergosterol synthesis. Interestingly, ergosterol was first discovered as a membrane component of *Claviceps Purpra* (a fungus that produces lysergic acid--the precursor of LSD) [72]. They have recently become a focus across a wide range of pathologies from cardiometabolic to oncologic and particularly neuropsychiatric [73]. They have been implicated in pathophysiologic processes related to depression, addiction, anxiety, stress responses, learning, and memory [74]. Indeed, many neuroleptics, antipsychotics, antidepressants, and neurosteroids have sigma-receptor activity [73].

As a molecular chaperone, the sigma-1 receptor plays many roles. It modulates cell survival and oxidative metabolism (via calcium signaling between mitochondria and endoplasmic reticula). It mediates inflammatory signaling in microglia and astrocytes across various neuropsychiatric disease models [75]. It also participates in the elaboration of proBDNF into its mature end-product [76] and potentiates nerve growth factor (NGF) secretion [77].

More importantly, sigma-1 forms heterodimer complexes with both 5HT-2A and D2 receptors to facilitate neurotransmission and dopamine/norepinephrine release, also potentiating NMDA antagonism [72]. Recently, sigma-1 has also been discovered to translocate to the nuclear envelope, acting as an epigenetic regulator. It has a dose-dependent interaction with histone deacetylase (HDAC) complexes, which regulate chromatin compaction and gene expression—a mechanism that appears to be particularly relevant to sigma-1's role in addiction [69,72]. Notably, like HDAC, mTORC1 is also believed to exert epigenetic regulation by modifying chromatin structure (via H3K36) and gene expression [78].

Long-lasting effects realized with only a few doses of any compound evokes the

notion of epigenetic modulation more than any other mechanism discussed in this review. Only a handful of psychedelics have been investigated for their sigma-receptor activity. DMT is a highly potent ligand for the sigma-1 receptor [79], having an order of magnitude greater affinity than ketamine [77]. Ibogaine's affinity for sigma-1 is roughly equivalent to ketamine's. However, it appears to have a much higher affinity for sigma-2 than 5HT-2A or any other endogenous receptor studied [80]. The specific functions of sigma-2 are enigmatic; however, they appear to be tangentially related to some of those discussed for sigma-1. The recent cloning of the receptor should engender significant discoveries in the coming decade [71]. Overall, the differential sigma receptor activity of ketamine and other hallucinogens may present another explanation for the duration of response.

CONCLUSION

Psychedelic drugs appear to hold significant promise in ameliorating a myriad of neuropsychiatric conditions. Achieving rapid and sustained responses without daily dosing of medication should be the benchmark for mental healthcare going forward. As Jung envisioned, for durable responses, pharmacology should be used as an adjunct to psychotherapy rather than a unitary measure. In this regard, psychedelics can already be viewed as a success. However, uncovering the mechanisms responsible for prolonging the response to rapid-acting antidepressants may be as important as the initial discoveries themselves. Though the answer is almost certainly multifactorial, inflammation, epigenetic regulation, opiate signaling, and neuroplasticity all appear to be promising avenues for investigation.

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