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Research Article

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Ketamine: Review and Hypothesis for Potential Use in Spinal Cord Injury

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Abstract

Spinal cord injury (SCI) affects approximately 40 million people each year worldwide and no effective medicine has been found to ameliorate the disabling effects of SCI. Psychoplastogens are a heterogenous group of medicines defined by their function rather than their chemical structure. These medicines catalyze the growth of new neurons (viz. neurogenesis) and stimulate the formation of new connections between neurons (viz. synaptogenesis). Examples of psychoplastogens include ketamine, psilocybin, and lysergic acid diethylamide (LSD).

Several psychoplastogens exhibit promise as potential therapeutic agents in the treatment of SCI. In pre-clinical studies, the psychoplastogen LSD aided in recovery from SCI. An anecdotal report suggests the psychoplastogen psilocybin assisted a paralyzed patient recover from SCI. Finally, other mycological psychoplastogens have also shown promise as treatments for SCI including Tricholoma matsutake (Pine mushroom), Hericium erinaceus (Lion's Mane), and Lignosus rhinocerotis (Tiger milk).

Racemic ketamine is an inexpensive general anesthetic, a rapid-acting antidepressant medication, and a psychoplastogen. This medication, which is safe when used in low doses, stimulates the growth of nervous system structures, thus making it a potential option for individuals who suffer from SCI. Based upon a review of the existing literature regarding the aforementioned psychoplastogens, we hypothesize that daily low dose racemic ketamine may assist in recovery from SCI. We recommend clinical trials to determine the efficacy, dosage range, and optimal dosing frequency for the treatment of SCI.

Keywords: *psychoplastogens, neurogenesis, synaptogenesis, neuroplasticity.*

1. Introduction

1.1. Spinal cord injury

Spinal cord injury (SCI) is an injury of the spinal cord which results from compression, incision, or contusion. This primarily affects young individuals; the average age of injury is 43 years [1]. As a result of SCI, the functions of the spinal cord are interrupted distal to the site of the injury, impacting long tracts including the corticospinal tract, the spinothalamic tract and posterior columns, as well as inter-neurons, subserving motor and sensory functions. Each year approximately 40 million people worldwide suffer from SCI, leading to serious disability among these individuals [2]. Indeed, the lifetime economic costs of SCI are significant and have been estimated to be $2.5 million per patient [1]. The cellular mechanisms of damage in SCI relate to several factors. Acutely, there is a prominent ischemia associated with injury, resulting in decreased energy to nervous system structures [3]. There is significant associated necrosis and apoptosis, with axonal and neuronal changes related to both the primary insult, as well as the associated secondary injury, such as alterations of voltage-sensitive sodium channels [4] and alterations in the local micro-circulation [5]. Moreover, a significant mechanism of injury relates to high levels of the neurotransmitter glutamate, which effects excitotoxicity, as well as oxidative damage and ischemia, with associated calcium-dependent nitric oxide synthesis effecting additional damage [6]. Indeed, SCI models in non-human primates reveal increases in excitatory amino acids (glutamate, aspartate) both acutely and with persisting levels [7]. There are data that show blockage/antagonism of the N-methyl-D-aspartate receptor (NMDAR) in animal models of SCI protects against cellular damage from trauma and ischemia [8], decreases edema [9] and generates functional improvement with blockade of a-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors [10]. Both axonal degeneration and demyelination occur due to a release of cytokines resulting in apoptosis [11] further facilitated by activity at opioid receptors [12]. Blocking opioid function with naloxone has been shown to improve outcomes in experimental models of SCI [13].

1.2. History of ketamine

Racemic ketamine was first synthesized in 1963 by scientists at Parke-Davis who were searching for an alternative to phencyclidine (PCP), a general anesthetic which can cause prolonged and severe postsurgical delirium. One of these scientists, Calvin Stevens, synthesized a series of PCP

derivatives and found one, which was subsequently named CI-581, that produced short-acting anesthesia. Today this medicine is known as *ketamine*. The first dose of racemic ketamine was administered intravenously to a human in 1964 [14]. Individuals who were administered this medicine subsequently described "strange experiences like a feeling of floating in outer space and having no feeling in their arms or legs." The wife of one of the clinical investigators who was administering ketamine coined the term "dissociative anesthetic" to describe this effect, and ketamine has subsequently been categorized in this way.

The U.S. Food and Drug Administration (FDA) approved racemic ketamine as a medicine for general anesthesia in 1970 and now it is classified as a Schedule III controlled substance [15]. Racemic ketamine has been on the World Health Organization's Essential Medications List since 1985 [16]. Racemic ketamine is a mixture of S(+)-ketamine and R(-)-ketamine. In Europe, S(+)- ketamine was approved in 1998 and is indicated for the induction and maintenance of general anesthesia. In 2019, S(+)-ketamine was approved as an antidepressant by the European Medicines Agency and by the FDA [15, 17]. For many years racemic ketamine was thought to be solely a synthetic medicine. Then, in 2020, researchers in Brazil discovered this same chemical is produced in nature by the fungus Pochonia chlamydosporia [18].

1.3. Ketamine's mechanism of action

Both in vitro and pre-clinical studies demonstrate racemic ketamine promotes neurogenesis [19, 20], synaptogenesis [21], and remyelination of neurons [22]. A number of mechanisms of action have been proposed to explain these changes. Racemic ketamine's mechanism of action was originally thought to result from its antagonism of glutamate binding to NMDA receptors. Glutamate is a non-essential amino acid and is the predominant neurotransmitter in the mammalian central nervous system (CNS).

Glutamate is also the major excitatory neurotransmitter in the human CNS. Glutamate signaling involves two families of receptors: metabotropic glutamate receptors (mGluRs) and ionotropic glutamate receptors (iGluRs). Both families are believed to play a role in the pathophysiology of chronic neuropsychiatric and neurodegenerative disorders. mGluRs are G-protein-coupled receptors (GPCRs) that initiate signaling cascades and/or cation influx upon glutamate binding. The iGluR subfamilies all share a common voltage-gated ion channel function and include the NMDA, AMPA, and kainate receptors [23].

Ketamine is a noncompetitive NMDAR antagonist but at low concentrations ketamine blocks only a fraction of NMDARs. At anesthetic doses, ketamine blocks a higher percentage of NMDARs, which produces different clinical effects [24]. In addition to its effects at NMDARs, ketamine persistently enhances AMPAR-mediated excitatory synaptic signaling. This effect involves activation of the mechanistic target of rapamycin (mTOR) kinase, inhibition of eukaryotic elongation factor 2 kinase, and enhanced brain-derived neurotrophic factor (BDNF) signaling via TrkB receptors [25-27].

Because ketamine induces ion channel blockade, it exerts actions on several receptors and channels. For example, ketamine binds to and inhibits hyperpolarization-activated cyclic nucleotide gated cationic channels that express the HCN1 subunit [28]. Ketamine also binds with mu, delta, and kappa opioid receptors. Ketamine influences the monoaminergic system by stimulating noradrenergic receptors and inhibiting the uptake of serotonin and dopamine. Ketamine also affects the cholinergic system by inhibiting nicotinic and muscarinic receptors [14, 29-30]. Ketamine also binds to sigma-1 receptors [31].

Glutamate reuptake occurs via dedicated transporters thereby preventing its accumulation at the synapse. High levels of extracellular glutamate produce abnormal synaptic signaling and neuronal excitotoxicity (i.e. degeneration of dendrites) along with cell death. Excessive glutamate also triggers neuroinflammation, which can result in additional damage to neurons [32]. Ketamine may reduce these effects by selective inhibition of glutamate binding to NMDARs.

As noted above, racemic ketamine is also a sigma receptor agonist. Sigma receptors, which were first isolated in 1982 [33], are non-opioid, non-phencyclidine receptors that contain two subtypes: sigma-1 and sigma-2 receptors. The sigma-1 receptor (Sig-1R) contains 233 amino acids whose sequence does not resemble any known mammalian protein but does have a 30% identity and 66% homology to a fungal protein known as C8-C7 sterol isomerase [34-35]. Sig-1R agonists amplify intracellular signals of other neurotransmitter systems [35] and stimulate the rapid release of BDNF [31, 36]. Ketamine binding to Sig-1R facilitates the release of BDNF, resulting in downstream trophic effects on the nervous system structures.

1.4. Pharmacokinetics of ketamine

Ketamine is an arylcycloalkylamine that exists as S(+) and R(−) isomers and is commonly marketed as a racemic mixture of the two (R, S-ketamine) [37]. The volume of distribution is large, with a weighted mean Vd of 252L/70kg [38] . Mean weighted clearance is 79L/hr and is best approximated with a three-compartment model, with one central compartment and two peripheral compartments [38].

Ketamine is metabolized by cytochrome P450 enzymes CYP 3A and 2B6, with extensive first-pass metabolism [39]. Oral bioavailability is poor, with intranasal and sublingual formulations having improved bioavailability [39]. The half-life of racemic ketamine is 2.1 - 2.5 hours [40-41]. The major metabolites are norketamine and dehydronorketamine (DHNK), which appear in venous blood about 10 and 30 min after administration, respectively. Norketamine produces similar effects to ketamine but has only one-third the potency of ketamine and a half-life of 1.3 hours; DHNK is only weakly active at the NMDAR, with limited pre-clinical activity [14, 40].

1.5. Ketamine dosing and bioavailability

When used for anesthesia, the initial IV dose of ketamine ranges from 1 - 4.5 mg/kg administered over 60 seconds for those 16 years old or older. A dose of 2 mg/kg is the average amount

required to produce approximately 5 to 10 minutes of anesthesia, with the onset of action in about 10 to 30 seconds and a duration of action lasting approximately 5 to 15 minutes. Once the dosage of ketamine reaches approximately 1 to 1.5 mg/kg given IV or 3 to 4 mg/kg administered intramuscularly (IM), a dissociative state occurs [42]. For the treatment of depression, ketamine is generally administered intravenously at a dose of 0.5 mg/kg. However, some patients may respond to doses as low as 0.1 mg/kg, and others may require up to 0.75 mg/kg. The medicine is conventionally administered over 40 minutes, but safety and efficacy have been demonstrated in sessions ranging from 2 to 100 minutes. Another option is intramuscular or subcutaneous administration, which have been demonstrated to be safe and effective. Additional routes of administration include transmucosal, intranasal, oral, and sublingual [43].

The bioavailability of ketamine depends upon the route of administration. Intranasal and SC administration approach 100% bioavailability. When injected IM, the bioavailability is 93%. Oral ingestion results in 17-24% bioavailability and increases to 30-32% with sublingual use [43-45].

1.6. Ketamine as a treatment for depression

In a 2000 randomized double-blind placebo-controlled trial, researchers at Yale University School of Medicine found the intravenous administration of a low dose (0.5 mg/kg) of racemic ketamine resulted in significant improvement in depressive symptoms within 72 hours, whereas placebo infusion had no effect [46]. More than a decade later, Lara and colleagues [47] administered a very low dose of sublingual (VLDS) racemic ketamine (10 mg) repeatedly every 2–7 days to 26 outpatients with refractory unipolar or bipolar depression. They found VLDS ketamine produced rapid and sustained improvement in mood, cognition, and sleep in 20 patients (77%) with only mild and transient light-headedness as a common side-effect. No euphoria, psychotic, or dissociative symptoms were reported. The authors concluded, “VLDS ketamine may have broad spectrum effects beyond its antidepressant properties, with rapid onset of action, high efficacy, good tolerability and low cost, allowing extended treatment as needed.”

1.7. Ketamine’s antidepressant mechanism of action

Several hypotheses have been offered to account for ketamine’s antidepressant mechanism of action. Abdallah and colleagues [48] describe a series of events that they suggest produce ketamine’s antidepressant effects including 1) blockade of interneuronal NMDA receptors, 2) disinhibition of pyramidal cells leading to a glutamate surge, 3) activation of AMPA receptors, 4) blockade of the excitotoxic extrasynaptic NMDA receptors, and 5) activation of intracellular signaling including mTOR and brain-derived neurotrophic factor (BDNF) pathways.

Kavalali and Monteggia [49] suggest blockade of NMDA receptors by ketamine deactivates eukaryotic elongation factor 2 (eEF2) kinase, which reduces eEF2 phosphorylation and increases translation of BDNF. These signaling pathways converge to produce increased levels of BDNF, which stimulate neurogenesis in the ventral hippocampus and synaptogenesis in the medial prefrontal cortex in rodent models [50-51]. According to the neurotropic hypothesis of depression, these neuroplastic changes reverse the atrophy of neurons associated with chronic stress or neuroinflammation, resulting in improvements in depression [52].

1.8. Ketamine as a psychoplastogen

In 2018 researchers at the University of California, Davis identified a class of medicines which increases levels of BDNF resulting in neuroplastic changes. They labeled these medicines “psychoplastogens" based on their ability to promote structural and functional neuroplasticity and their ability to effectively treat neuropsychiatric disorders [53-54]. Ketamine was recognized to be one of these psychoplastogens, along with a group of psychedelic medicines that includes Lysergic acid diethylamide(LSD), psilocybin, and others [55-56].

Olson [56] describes a number of structural and functional neuroplastic changes associated with psychoplastogens. The proposed synaptic mechanism of action for these changes involves the release of glutamate from presynaptic glutamatergic neurons, followed by AMPA receptor activation, leading to increased secretion of brain-derived neurotrophic factor (BDNF), resulting in increased neurogenesis and synaptogenesis. These neurological changes are hypothesized to be capable of treating a range of neuropsychiatric and neurodegenerative diseases [54].

1.9. Treatments of spinal cord injury with psychoplastogens

Although numerous pharmacological therapies have been explored to ameliorate SCI-related damage, no single treatment has been found that significantly improves serious long-term sequelae of SCI, such as paralysis, sensory loss, spasticity, or incontinence [57]. Encouraging results have been reported, however, in both in vitro and in vivo pre-clinical studies with psychoplastogens. One possible mechanism by which psychoplastogens could facilitate recovery from SCI is by increasing levels of BDNF.

Increased BDNF levels have been demonstrated to facilitate recovery from SCI in rodent studies. Intrathecal administration of BDNF following spinal cord injury enhanced recovery [58-59] as did intrathecal transplantation of human neural stem cells that over-express BDNF [60]. Transplantation of human stem cells that hyper-secrete BDNF resulted in structural changes in the brain and spinal cord, which are associated with improved functional outcomes in acute SCI [61].

1.9.1. *LSD and SCI*

LSD was first synthesized by Swiss chemist Albert Hofmann in 1938 while attempting to find a medicine that stimulates the respiratory and circulatory systems. Lysergic acid is the nucleus of the alkaloids of ergot, a fungus that grows on rye and related plants. Five years after his initial synthesis of this medicine, Hofmann accidentally ingested a small amount, possibly through his skin, and became the first person to experience LSD’s psychedelic effects [62]. This medicine was later demonstrated to exert at least some of its effects by binding to the 5HT2A receptor [63]. Nearly four decades later, de Santis and Kemali [64] found the administration of LSD to isolated hemisected frog spinal cord resulted in a significant

enhancement of spontaneous dorsal and ventral root activity. However, lisuride, a 5-HT2A agonist and LSD homologue which does not possess psychedelic properties, had no effect, suggesting additional mechanisms are required for the observed trophic nervous system findings of LSD. Arvanian et al. [65] found a combination of LSD and the protein Neurotrophin-3 (NT-3) facilitated recovery in rats with induced SCI. Improvement, which was defined as increased kicks during swimming and increased rearing behavior, was noted in rats that received combination treatment with both LSD and NT-3, but not in rats receiving LSD or NT-3 alone. The authors concluded: "Our results suggest this combination treatment may be a promising new strategy for facilitating recovery from moderate spinal cord injury."

1.9.2. *Psilocybin and SCI*

Psilocybin (4-phosphoryloxy-N,N-dimethyltryptamine) is a substituted indolealkylamine found in hundreds of mushroom species around the world. Psilocybin was first isolated from the mushroom Psilocybe mexicana in 1957 by the same Albert Hofmann who created LSD [66]. Following ingestion, psilocybin is converted to psilocin, which is the primary active ingredient in the mushroom [67]. Psilocybin has been shown to produce structural and functional neuroplastic changes in the brain's frontal cortex. Shao and colleagues [68] reported a single dose of psilocybin produced a ~10% increase in spine density and spine size in the frontal cortex of mice. This structural remodeling occurred within 24 hours of the dose and persisted for 1 month. Although psilocybin's effects on the spinal cord have not been well studied, an anecdotal report in the lay literature describes JH, a 33-year-old male who was injured in a snowkiting accident in November 2014. As a result of the accident, JH fractured nine vertebrae and was paralyzed below the chest. Following surgery to decompress his spine and fuse five vertebrae, he was able to wiggle one toe. In January 2015, the patient was transferred to Craig Hospital in Denver, Colorado, an institution devoted to spinal cord and brain injuries, where he underwent 5 months of physical therapy. By July 2015, the patient was able to ambulate with the help of a walker. Then, after ingesting psilocybin mushrooms in a recreational setting, he began experiencing improved muscle function in his legs. Subsequently, he achieved the ability to walk with just a cane and is now able to ski and mountain bike [69]. The use of the psychoplastogen psilocybin with standard physical therapy and rehabilitation was associated with clinical improvement in this patient. While not conclusive, the improvement is consistent with reported neuroplastic changes following the administration of psychoplastogens in both in vitro and pre-clinical in vivo studies.

1.9.3. *Mushrooms and SCI*

Liu and colleagues [70] found the edible and medicinal mushroom *Tricholoma matsutake* helped repair SCI by promoting axon regeneration and reducing neuroinflammation. They chose this mushroom based on the finding *Tricholoma matsutake* polysaccharides (TMP) exhibit strong anti-inflammatory and anti-oxidative effects. Using cultured nerve cells and spinal cord clamp injured mice, they found TMP promoted neuronal proliferation and neurite growth in cultured cells and inhibited neuroinflammation by reducing TNFα and IL-6 levels in a concentration-dependent manner. In mice, TMP improved the morphology of the spinal cord and promoted the recovery of motor function within one week of SCI. Also, TMP promoted the growth of neurons and neurites in the injured spinal cord. TMP thus promoted the regeneration of neuronal cells in vivo and in vitro, and significantly inhibited neuroinflammation allowing improved clinical function in mouse models. Samberkar and colleagues [71] found the mushrooms *Hericium erinaceus* (Lion's Mane) and *Lignosus rhinocerotis* (Tiger milk) stimulated neurite outgrowth in dissociated cells of brain and spinal cord from chick embryos. These effects were dose dependent. These findings from both in vitro and in vivo studies demonstrate neuroplastic changes in the CNS and improvement in SCI following treatment with psychoplastogens such as LSD,
psilocybin, *Tricholoma matsutake*, *Hericium erinaceus*, and *Lignosus rhinocerotis*.

2. Hypothesis

We hypothesize that racemic ketamine may assist in recovery from SCI.

3. Evaluation of the hypothesis

Racemic ketamine has been suggested as a possible treatment for a wide range of neurological disorders including dementia, Parkinson's Disease, multiple sclerosis, stroke, status epilepticus, traumatic brain injury, and anti-NMDA receptor encephalitis, [72-73]. Racemic ketamine is an approved medicine both in Europe and the U.S. which creates an opportunity to investigate this medicine as a potential treatment for SCI.

LSD and psilocin bind to tropomyosin receptor kinase B (TrkB), the receptor for brain-derived neurotrophic factor (BDNF), and the neuroplastic effects of psychedelics depend on BDNF binding to TrkB [74]. Similarly, racemic ketamine's neuroplastic effects are also dependent upon BDNF release and binding to TrkB [27, 75]. Thus, racemic ketamine shares a common mechanism of action with LSD and psilocybin that includes increasing levels of BDNF with resulting neuroplastic changes. Elevated levels of BDNF have been demonstrated to improve recovery from SCI.

Given racemic ketamine's ability to stimulate neurogenesis and synaptogenesis, as well as reduce neuroinflammation, in conjunction with its shared mechanism of action with other psychoplastogens that have a demonstrated ability to improve SCI, it would appear ketamine would be an excellent candidate to study as a potential treatment for SCI.

4. Discussion

Psychoplastogens are medicines that catalyze structural and functional neuroplasticity resulting in improvement in psychiatric disorders such as depression, anxiety, and addictions. The psychoplastogens described in this article exhibit additional potential benefits that include reducing neuroinflammation and oxidative stress [76]. The psychoplastogens LSD, psilocybin, *Tricholoma matsutake*, *Hericium erinaceus*, and *Lignosus rhinocerotis* have been

shown to repair SCI by stimulating axon regeneration, neurite outgrowth, and reduction in neuroinflammation. Racemic ketamine is a psychoplastogen with a long history of safe use, both as a general anesthetic and as a treatment for depression. The observation that several neuroplastogens derive from fungal origins raises the possibility that these medicines share common therapeutic mechanisms of action. Their previously described effects on BDNF appear to be one shared mechanism of action. Another common feature of these medicines involves their action at Sig-1R. Indeed, the Sig-1R agonist cutamesine increases the release of BDNF resulting in increased levels of extracellular BDNF [77]. Racemic ketamine is also a Sig-1R agonist that stimulates the rapid release of BDNF [31, 36].

Based on the findings of this review, research into the daily use of racemic ketamine as a treatment for SCI appears warranted. Studies exploring not only the efficacy, but also the optimal dosage range, route of administration, frequency of dosing, and potential side effects would be beneficial. Also, studies examining various lengths of treatment could help identify the duration of treatment required to experience improvement. Given the slow rate of growth of neurons, it is possible that such treatment may need to continue for 6-12 months, or even longer, for benefits to be observed. Further work with ketamine as a potential treatment for SCI may lead to the discovery of improved therapeutics to aid those suffering from SCI.

Conflict of interest

The authors have no conflict of interest.

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