The Use of Ketamine as Therapy for Depression

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ABSTRACT

Depressive disorder is still a significant problem in several developed countries and is morbidity caused by mental disorders. With the development of science, now discovered the unique pharmacodynamic properties of ketamine, which is used as an antidepressant. As we know in clinical practice, ketamine is used for anaesthesia, analgesia, sedation, and chronic pain management. Rapid-onset antidepressants resulted from increased levels of BDNF in the hippocampus. Extracellular glutamate agents are not new for the treatment of depression. According to the neurobiology view, depression is a monoaminergic phenomenon, so this is the impetus for discovering a new generation of antidepressants. Ketamine can be given intravenously in subanesthetic doses. Still, monitoring must be carrying in therapy administration because of the possible side effects such as hypersalivation, tachycardia, increased systemic arterial pressure, and intracranial pressure.

Introduction

Depression has become one of the major problems in modern society and the number 3 cause of disability globally. Advances in conventional antidepressant treatment only waned in a few weeks, resulting in widespread resistance to treatment. Since half a century ago, many researchers began to better understand the pathophysiology and psychopathology of depression. There are many clinical laboratory studies to determine the mechanism and clinical properties of ketamine. Ketamine is a structural analogue of the dissociative anaesthetic and recreational drug phencyclidine (PCP). Like phencyclidine, ketamine causes analgesia and amnesia without the cardiovascular and respiratory depression associated with general anaesthesia. In administration during surgery is usually combined with a benzodiazepine to reduce the psychological symptoms that occur.

Subanesthetic dosing can use for acute and chronic pain management, sedation, and treatment of major depression. Ketamine can produce an antidepressant effect, a short-term dissociative effect that can affect consciousness and perception. Ketamine acts on a cascade of intracellular signalling pathways that generate an inflammatory response, which is involved in the pathophysiology of depression. Depression occurs due to monoamine deficiency, and increased glutamate and its centre are present at the N-methyl-D-aspartate (NMDAR) receptor.

Ketamine has been shown to have antidepressant effects and has recently approving to treat therapeutic resistant depression, with clear indications, contraindications, and treatment regimens.

Clinical evidence of ketamine as an
antidepressant

Ketamine as an anaesthetic has been developed in clinical practice because other significant effects have been found, namely as an antidepressant. The effect of ketamine as an antidepressant is related to the type of change in brain oscillations. Ketamine modulates glucose metabolism in the brain that affects anxiety and depression, and effectively treats resistant depression. Physiologically, this mechanism is maintained by the supply of energy to the population of neurons. Several studies conclude that ketamine rapidly and significantly reduces suicidal tendencies and anxiety, and this effect can last for one week. Mood depression is frequently reported in postoperative patients; small doses of ketamine (0.5 mg kg\(^{-1}\)) at induction of anaesthesia can reduce mood depression by increasing serum brain-derived neurotrophic factor (BDNF).\(^2\)

**Neurobiology and antidepressant properties of ketamine**

Two hypotheses are linking cortical synaptic to ketamine. Ketamine blocks NMDA on GABA interneurons, causing disinhibition of pyramidal structure-laden activity in the cortex, thereby increasing receptor signalling that triggers a cascade of pathways including \(-\)amino-3-hydroxy-5-methylisoxazole-4-propionate (AMPA) receptor activation, secretion brain-derived neurotrophic factor (BDNF), and mammalian target activation of rapamycin signalling (mTOR); NMDA receptor antagonists inhibit eukaryotic elongation factor 2 kinase and increase cortical synaptic connectivity. Ketamine reverses CSP in the prefrontal cortex, hippocampus, and NAc within one day of administration via postsynaptic glutamate activation with upregulation of neurotrophic signalling and increased protein synthesis, providing restoration of synaptic connectivity lasting for days or even weeks. The antidepressant properties of ketamine may also be due to its effect on mitochondrial energy metabolism.\(^1,5\)

![Image of disconnection hypothesis](image.png)

**Emerging antidepressant mechanism**

**NMDA Receptors as Mediators**

Ketamine is a non-competitive NMDA receptor antagonist that causes the main antidepressant effect. Then proceed with inhibition of glutamatergic input to GABA interneurons and result in glutamatergic disinhibition resulting in decreased feedback and increased glutamatergic excitatory transmission.\(^5,6\)

**Non-NMDA Mediators**

The neurochemical Cascades and Other Mechanisms

Other mechanisms involving neurochemistry, such as glycogen synthase kinase-3 (GSK3) and mTOR, mediate the effects of fast-acting antidepressants. Ketamine also modulates TrkB signalling, which activates BDNF via a complex cascade involving the \(-\)amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor (AMPAR). The dopamine system is also involved in modulating the phenotypic markers of depression. It has also been found that they are potential targets in the mechanisms of fast-
acting antidepressants, for example, the suicide receptor ketamine. Another component involved in the antidepressant effect is the eukaryotic elongation factor 2 kinase (eEF2K), which is the key to mediating the effects of fast-acting antidepressants.5,6,7

**Proposed mechanisms mediating ketamine rapid antidepressant effects**

Figure 2. Main mechanisms underlying non-NMDA-mediated effects of ketamine.

**Potential mechanism of antidepressant of ketamine**

Potential mechanism of antidepressant of ketamine: 2 kinase (eEF2K), which is the key to mediating the effects of fast-acting antidepressants.5,6,7

**Side-effects of ketamine**

Several side effects occurring when giving ketamine are acute psychiatric side effects; anxiety followed by agitation or irritability, euphoria or mood elevation, delusions or unusual thoughts, panic, and apathy; psychotomimetic effects: dissociation, followed by perceptual disturbances, strange or abnormal sensations, derealization, hallucinations, strange or unreal feelings, and depersonalization. Cardiovascular effects of ketamine are increased blood pressure and heart rate. No long-term psychotomimetic side effects have to report. 3

**Conclusion**

Currently, cases of depression are still the biggest psychopathological problem in modern society. Handling depression is also still not satisfied so that cases of morbidity due to mental disorders are still high. Currently, there are psychopharmacology used in the treatment of depression that are effective. Ketamine, in addition to functioning as an anaesthetic and pain management, research and clinical trials prove that ketamine use as an antidepressant that has specific functions, modulation of receptors, and induction of
Despite much controversy regarding the use of ketamine, several clinical trials have proven the effectiveness and tolerance of ketamine as an antidepressant drug. During the administration of ketamine should be monitored for side effects—further research needs to apply ketamine as a treatment for depression.

References