



American College of Neuropsychopharmacology

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Animal Study Suggests Antidepressant Effects of Ketamine can be Separated from Potential Side Effects

New preclinical evidence was put forward by investigators in a series of presentations at the recent meeting of the American College of Neuropsychopharmacology suggest that the a metabolite of ketamine can produce antidepressant-like effects in a mouse model of depression. The metabolite is produced when ketamine is broken down in the body. This finding may lead to further research to better understand ketamine's efficacy in depression and its potential side effects.

Recent findings show that ketamine, which is used in both human and veterinary medicine as an anesthetic, has rapid and potent antidepressant effects in humans, even in those resistant to the beneficial effects of more traditional antidepressants. This finding has raised hope that ketamine may represent a new treatment option to help those suffering from the debilitating symptoms of depression. However, ketamine has euphoric effects which have been associated with abuse potential – though typically at much higher doses than are used to treat depression. Ketamine can also induce dream-like states and perceptual changes. This has sparked a race to better understand how ketamine may contribute to anti-depressant effects, and to determine whether potential side effects can be separated from its beneficial antidepressant effects.

Ketamine is composed of two different isomers, called R-ketamine and S-ketamine, which are mirror images of each other. These two components of ketamine are converted in the body into R- and S-metabolites that, potentially, can have different actions. In his presentation, Dr. Kenji Hashimoto showed that in rodents, the antidepressant-like behavioral effects of ketamine may be related to the actions of R-ketamine and ketamine metabolites. Remarkably, one of these metabolites, S-norketamine, demonstrated in rodents that antidepressant-like effects in the absence of the motor stimulation effects which may be seen after ketamine treatment or recreational use. In a related presentation, Dr. Irving Wainer showed that another ketamine metabolite, hydroxynorketamine (HNK), also has potent antidepressant effects but does not show motor stimulation effects. It should be noted that the observations were in animal studies, which are not necessarily reproducible in humans. Additional studies in humans are needed to better understand the efficacy and safety of R-ketamine, S-norketamine and other ketamine metabolites in humans.

Dr Jaz Singh presented clinical data from a phase 2 study with intranasal S-ketamine showing a dose response in depressed humans who had not responded to conventional antidepressant drugs, and the efficacy persisted for 8 weeks after the last dose. Dissociative effects were dose dependent, began shortly after start of dosing, resolved in < 2 hours, and significantly attenuated with multiple dosing.

Finally, Dr. Lisa Monteggia provided new insights into how ketamine may act in the brain to exert antidepressant effects. She showed that ketamine activates the production of new proteins in nerve cells. These proteins play a role in encoding new memories and other information by brain cells. This suggests that ketamine may improve the function of brain circuits involved in mood regulation.

These findings suggest that R-norketamine, HNK and other closely related drugs could have antidepressant effects like those of ketamine but without its negative side effects. The findings also suggest that drugs that modify the ability of brain cells to produce new proteins could represent an entirely new class of antidepressant drugs.

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