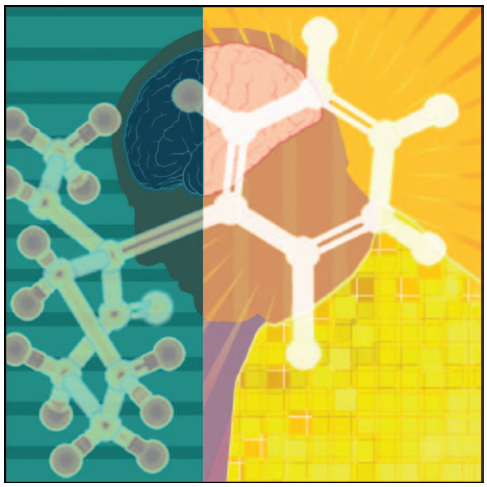
# Ketamine Metabolomics in the Treatment of Major Depression

Monique van Velzen, Ph.D., Albert Dahan, M.D., Ph.D.

ANESTHESIOLOGISTS are well aware of the fact that some of the drugs they frequently use undergo significant metabolism and that the metabolites of these drugs may have additional effects depending on the setting or the endpoint that is measured. One important example is morphine. Morphine is rapidly metabolized into morphine-3-glucuronide and morphine-6-glucuronide. Morphine-6-glucuronide is an opioid receptor agonist that has no effect in healthy patients but will cause additional pain relief and excessive sedation in a patient with renal failure (due to the inability to clear the metabolite), whereas in an experimental setting, it may have hyperalgesic properties.[1] Ketamine is another example. Upon its administration, it is rapidly metabolized in the liver by microsomal enzymes into a series of compounds of which norketamine and hydroxynorketamine are considered most important. In line with the observations with morphine, the contributions of ketamine's metabolites to effect may vary depending on the specific endpoint that is examined. In this issue of ANESTHESIOLOGY, Paul *et al.*[2] examined the effect of (*R,S*)-ketamine and its metabolites (*R,S*)-norketamine and (*2S,6S*)-hydroxynorketamine on a molecular pathway that is involved in the *antidepressant* effects of ketamine. They show that ketamine increases the levels of the activating phosphorylated form of mammalian target of rapamycine (mTOR; a protein kinase involved in protein synthesis, synaptic plasticity, and neurotrophic signaling) and cognate signaling kinases in prefrontal cortex tissue of the rat and in an *in vitro* cell model. Importantly, its two metabolites, norketamine and hydroxynorketamine, had similar effects compared with the parent compound, and the effects occurred at relevant concentrations. This indicates that both metabolites contribute significantly to the mTOR-mediated effects of ketamine. In addition, the authors relate this effect on mTOR to the inhibition of the $\alpha_7$-subtype of the nicotinic acetylcholine ($\alpha_7$nACh) receptor.



***"Although hydroxynorketamine does not contribute to the anesthetic effects of ketamine [...], it does have an important contribution to ketamine's antidepressant behavior [...]."***

The use of ketamine as an antidepressant may not be well known to all of our colleagues. Anesthesiologists use ketamine predominantly as an anesthetic or induction agent and as an analgesic in acute and chronic (neuropathic/cancer) pain, until recently the two most important indications for ketamine treatment. Studies performed by psychiatrists and behavioral scientists in patients with clinical depression and studies in chronic pain patients showed that ketamine has significant and long-lasting antidepressant effects with a rapid onset of action.[3–5] In 2000, Berman *et al.*[4] were the first to examine the effect of ketamine on depression in a small, placebo-controlled, proof-of-concept study. In nine patients with major unipolar or bipolar depression, ketamine (0.5 mg/kg infused slowly more than 40 min), but not placebo, produced rapid mood improvement that peaked after 72 h. This is an important finding as commonly used antidepressants take 2 to 12 weeks before any mood improvement becomes apparent. Various later studies replicated these exciting results (reviewed in the study by Murrough[5]). Currently, ketamine is used for a restricted number of psychiatric indications related to therapy-resistant mood impairments, and its administration is often in close cooperation with anesthesiologists, who are most knowledgeable of the complexities of this drug.

Recent evidence suggests that neuronal atrophy and loss of synaptic density in areas of the brain that control mood, cognition, and emotion underlie the pathophysiology of depression.[6] The brain areas involved include the prefrontal cortex and the limbic system. Li *et al.*[7] were the first to elucidate the molecular mechanism of ketamine-induced antidepression.

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They showed that by the rapid activation of the mTOR pathway in the rat prefrontal cortex and the subsequent increase of multiple synaptic signaling proteins, dendritic spine density (synaptogenesis), and synaptic activity, ketamine induces behavioral responses indicative of mood improvement and antidepression. As stated earlier, the study by Paul *et al.*[2] demonstrates that the activation of the mTOR signaling pathway is not restricted to ketamine but that also norketamine and hydroxynorketamine contribute to this antidepressant pathway by inhibition of the $\alpha_7$nACh receptor.

Moaddel *et al.*[8] showed previously that although (*2S,6S*)-hydroxynorketamine is a potent inhibitor of the $\alpha_7$nACh receptor at concentrations at which (*R,S*)-ketamine has no effect, it is not active at the *N*-methyl-D-aspartate (NMDA) receptor. Inhibition of the NMDA receptor is held responsible for the state of dissociative anesthesia induced by ketamine (although other receptor systems may play a role as well) and its many side effects, including psychedelic effects.[9] Indeed, hydroxynorketamine lacks anesthetic activity.[8,10] These data therefore confirm that the relative metabolite contribution to ketamine effect varies, depending on the pharmacological endpoint that is examined. Although hydroxynorketamine does not contribute to the anesthetic effects of ketamine (due to absence of effect at the NMDA receptor), it does have an important contribution to ketamine's antidepressant behavior (due to its potent effect at the $\alpha_7$nACh receptor). In fact, the possible lack of NMDA-receptor-related side effects makes hydroxynorketamine an attractive alternative to ketamine as an antidepressant in humans.

Ketamine's complexity not only relates to its metabolic profile, but equally important is the fact that ketamine is a racemic mixture containing equal parts of (*S*)- and (*R*)-isomers (the (*S*)-isomer is commercially available in some countries, in all others, including the United States, the racemic mixture is marketed). Studies show that these isomers have distinct potencies with respect to their anesthetic properties: the (*S*)-isomer has a fourfold greater affinity for the NMDA receptor compared with the (*R*)-isomer. Interestingly, in animal models of depression, Zhang *et al.*[11] showed recently that the (*R*)-isomer is more potent than the (*S*)-isomer in producing rapid (within 1 day) and long-lasting (at least 7 days) antidepressant behavior. Possibly, this relates to the differences in receptor activity of the two isomers at the $\alpha_7$nACh receptor. The authors, however, did not study the metabolites of the two ketamine enantiomers. Paul *et al.* studied the (*2S,6S*)-hydroxynorketamine and not the (*2R,6R*)-isoform or the racemic mixture, a decision based on the fact that the (*2S,6S*)-hydroxynorketamine isomer was more potent compared with the other two compounds. Although both studies show the importance of enantioselectivity, it remains unknown how the data in the study by Zhang *et al.* relate to those in the study by Paul *et al.* The former only presented behavioral efficacy data and Paul *et al.* gave no behavioral or quantitative data on efficacy (and toxicity) of the different hydroxynorketamine isoforms. Further studies are required to assess the relative roles of the different ketamine, norketamine, and hydroxynorketamine enantiomers in the activation of the mTOR pathway and behavioral changes in animal models of depression. The aim of such studies would be to produce an agent that has potent and rapid antidepressant effects but is without the typical ketamine side effects. The studies not only by Paul *et al.* but also by Zhang *et al.* are the first steps and certainly point us into the right direction.

## Competing Interests

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## Correspondence

Address correspondence to Dr. Dahan: a.dahan@lumc.nl

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