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. 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. 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 rapamycin (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.

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. In 2000, Berman et al. 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). 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. The brain areas involved include the prefrontal cortex and the limbic system. Li et al. were the first to elucidate the molecular mechanism of ketamine-induced antidepressant effects.
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 antidepressation. As stated earlier, the study by Paul et al. demonstrated 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 α7nACh receptor.

Moaddel et al. showed previously that although (2S,6S)-hydroxynorketamine is a potent inhibitor of the α7nACh 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. Indeed, hydroxynorketamine lacks anesthetic activity. 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 α7nACh receptor). In fact, the possible lack of NMDA-receptor-related side effects makes hydroxynorketamine an attractive alternative to ketamine as an antidepressant in humans.