Ketamine Analgesia and Psychedelia: Can We Dissociate Dissociation?

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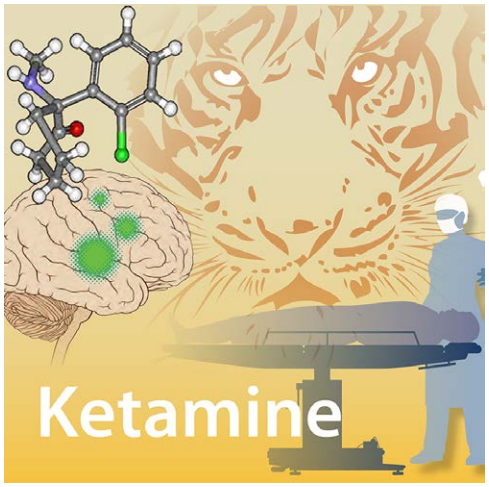
Ketamine is arguably the most interesting drug in our armamentarium. Depending on the dose and setting, ketamine can be used as an anesthetic, analgesic, antidepressant, psychedelic, or psychotomimetic (*e.g.*, to model psychiatric disorders such as schizophrenia). But what is the interrelationship of these psychoactive properties? Are they all reducible to a single and fundamental cause? Or do they represent a constellation of dissociable traits with distinct underlying mechanisms? In this issue of Anesthesiology, Olofsen *et al.* report a study that attempts to dissect the antinociceptive and psychedelic effects of ketamine.[1]



"… if [ketamine] works, who cares whether the analgesic and psychedelic effects are mechanistically distinct?"

The story of ketamine (or CI-581, as it was then known) began in the 1960s, when it was synthesized as an analog to mitigate the profound and prolonged emergence of delirium associated with phencyclidine. Clinical pharmacologist Dr. Edward Domino and anesthesiologist Dr. Guenter Corssen, two faculty members at the University of Michigan Medical School (Ann Arbor, Michigan), were the first to study ketamine in human patients.[2] After hearing of the unusual disconnection from the environment induced by ketamine, Domino's wife suggested that it be described as a "dissociative anesthetic." This phrase appeared in the first publication describing the clinical effects of ketamine anesthesia[3] and continues to be used today. Focusing on the dissociative effects of this drug is warranted because, although ketamine evokes numerous canonical traits of the psychedelic experience, the intensity of the dissociative experience far exceeds that induced by serotonergic counterparts such as psilocybin.[4]

Another reason it is important to highlight this signature feature of dissociation is that it could account for the other observed effects of ketamine. Perhaps pain, for example, is attenuated during exposure to ketamine because the self does not feel connected to the body that might be encountering the noxious stimulus. But if it works, who cares whether the analgesic and psychedelic effects are mechanistically distinct? The answer is that if these effects can be mechanistically differentiated, then it might be possible to design new drugs that can accomplish the analgesic (or antidepressant) actions of ketamine without the psychedelic and dissociative effects, which can be dysphoric for many. Along these lines, a laboratory study of methylenedioxymethamphetamine (commonly referred to as "MDMA" and colloquially known as "ecstasy") showed that the neural mediators responsible for pro-social effects and drug reward effects were distinct.[5] Incidentally, we, as a field, should be proud that an anesthesiologist, Dr. Boris Heifets from Stanford University (Stanford, California), conducted that study. In sum: understanding the dissociative effects of ketamine is of central importance to its neuropharmacology, and determining if dissociation and analgesia (or other effects) are mechanistically distinct is important for future drug discovery.

The approach of Olofsen *et al.* to address this question was to reanalyze a study of ketamine in 17 males.[1] The original study was a four-armed randomized trial,[6] but for this *post hoc* analysis, only two groups were investigated. One group received racemic ketamine, and another received S-ketamine, both with escalating infusion rates. During infusion, investigators assessed pain thresholds (antinociceptive effects) and perceptual disturbances (psychedelic effects). Blood drawn from an arterial catheter was used to measure plasma concentrations of ketamine and its metabolite norketamine; pharmacokinetic/pharmacodynamic models were generated. The overall goal was to identify the

Image: A. Johnson, Vivo Visuals Studio.

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effect-site drug concentration at which antinociceptive or psychedelic effects appeared. What the investigators found was that the model for the antinociceptive effect of ketamine and the model for the psychedelic effect of ketamine were not statistically distinguishable. Furthermore, including both endpoints in the same model improved its performance. The conclusion was that the antinociceptive and psychedelic effects of ketamine co-appear, suggesting interdependence and a common underlying mechanism. These findings, however, are not consistent with the results of previous work, including that from the authors. For example, Gitlin *et al.*[7] administered 2 mg/kg IV ketamine to 15 healthy volunteers and identified distinct models for analgesia and dissociative effects, suggesting independence and distinct underlying mechanisms. The Discussion section in the article from Olofsen *et al.*[1] appropriately addresses the many methodologic differences between their work and that of others as a way of accounting for the divergent findings.

So, what is the next stop on the ketamine trip? First, back to the laboratory. The most definitive way to address whether the psychedelic and analgesic effects of ketamine have distinct mechanisms is to dissect them based on receptors and/or neural circuits. As noted, the work on methylenedioxymethamphetamine is an encouraging precedent.[5] Furthermore, since the onset time for analgesic and psychedelic effects is important for investigations in humans, it is important to remember that ketamine has complex and fast dynamics in the human cortex. For example, ketamine anesthesia is associated with rapid alternation of low-frequency and high-frequency electroencephalographic signals, accompanied by shifts in complexity and functional connectivity.[8–10] Last, for those who are wondering how to assess psychedelic effects in animal or translational models, neurophysiologic findings such as increased complexity or altered cortical oscillations that correlate with psychedelic phenomenology in humans can also be identified in the rodent brain during exposure to subanesthetic ketamine.[11] Collectively, this line of investigation can yield important scientific contributions and is aligned with a wider trend of synthesizing nonhallucinogenic analogs of psychedelic drugs that have therapeutic potential, as has been recently done with ibogaine[12] and lysergic acid diethylamide (known widely as "LSD").[13]

In conclusion, the work of Olofsen *et al.*[1] challenges us to take the next step in basic, translational, and clinical research. Importantly, the healthy controversy surrounding ketamine in our field is connected to a much broader and more intense dialog of whether the apparent therapeutic effects of psychedelic drugs such as psilocybin or dimethyltryptamine are necessarily linked to altered states of consciousness *per se*, or whether therapeutic benefit can ultimately be dissociated from dissociation and other dimensions of the psychedelic experience.

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Competing Interests

Dr. Mashour is a consultant for TRYP Therapeutics (San Diego, California); however, his consulting is not related to ketamine.

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