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HOT TOPICS

NMDA-receptor independent actions of ketamine: a new chapter in a story that's not so old

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It has been nearly two decades since ketamine was introduced as a rapid acting antidepressant with good clinical efficacy in subjects who failed to remit in response to more conventional therapies [1]. Given it's potential for abuse and a litany of deleterious consequences in long-term ketamine users, serious questions remain about the utility of ketamine therapy. Yet, for many with intractable depression, ketamine provides considerable benefits. Hence the question: is there some substance that has the actions of ketamine, without being ketamine. To answer this, we must determine how ketamine works as an antidepressant.

Ketamine carries the epithet, "NMDAR antagonist." However, high-throughput screens have shown that most drugs in common use have multiple targets, and ketamine is no exception. Furthermore, many NMDAR antagonists have entered clinical trials for depression, but none have displayed the rapid, robust and long-acting antidepressant effects of ketamine [2]. (*R*)-Ketamine has a fourfold decrease in affinity for the NMDAR compared to its (*S*)-enantiomer yet shows stronger and longer-lasting antidepressant effects in preclinical models of depression, strengthening the hypothesis that a NMDAR-independent mechanism may be responsible for much of ketamine's antidepressant action [1]. A metabolite derived from (*R*)-ketamine also displays antidepressant effects in murine models of depression independent of the NMDAR [1]. These findings are tempered by the apparent antidepressant efficacy of esketamine in clinical trials. To address these apparent contradictions and to parse the molecular sites of ketamine action, we have turned to a simple cellular system with a straightforward biological reporter for antidepressant action.

Using this model system, we recently identified one NMDAR-independent mechanism that may contribute to ketamine's antidepressant effects. Every antidepressant examined thus far translocates $G\alpha_s$ from lipid rafts to the non-raft membrane regions, where it enjoys a more facile and productive relationship with adenylyl cyclase, increasing cAMP production. $G\alpha_s$ translocation can be assayed directly, by cellular fractionation, or indirectly by determining mobility of a fluorescent $G\alpha_s$ with fluorescence recovery after photobleaching (FRAP) and/or by measuring augmented cAMP production [3–5]. While most antidepressants require a 3-day incubation with cells to achieve this effect, a 15-min treatment of ketamine was sufficient to translocate $G\alpha_s$ from lipid rafts to non-raft regions. This "antidepressant biosignature" also included increased FRAP and elevated cAMP. Associated downstream subcellular events consistent with elevated cAMP; phosphorylation of cAMP related proteins and expression of BDNF were also evoked by 15-min ketamine treatment. Ketamine produced similar results between 1 and 10 μM. The former reflects plasma concentrations in patients and the latter, tissue concentrations in rodent studies. The increase in cAMP was maintained after near complete elimination of the NMDAR within the cells.

This leaves us in the position of revisiting questions about both the mode and site of ketamine action. GABA and glutamate systems have been implicated in ketamine action [1]. Perhaps ketamine exerts both pre- and post-synaptic effects and modulates multiple signaling systems in neurons and glia. Given the short half-life of ketamine, perhaps circuits are modulated in a long-term manner. Possibly, akin to antidepressants [6], ketamine or a metabolite associates with a membrane compartment where, sheltered from degradation, it enjoys a longer course of action.

Certainly, it is unsatisfying to end any document, even one so cursory as this, with more questions than answers. Nonetheless, it is the pursuit of those questions that will evoke progress that provides relief to those who suffer from depression. A kernel of hope may reside in the discovery of a single biologic hallmark, $G\alpha_s$ translocation, that provides commonality to ketamine and traditional antidepressants. Developing novel compounds that target the translocation of $G\alpha_s$ from lipid rafts and others we have learned from ketamine, may usher in a new era of rapid acting, safer and more effective therapy.

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REFERENCES

1. Zanos P, Moaddel R, Morris P, Riggs L, Highland J, Georgiou P, et al. Ketamine and ketamine metabolite pharmacology: insights into therapeutic mechanisms. Pharmacol Rev. 2018;70:621-660.
2. Newport D, Carpenter L, McDonald W, Potash J, Tohen M, Nemeroff C. Ketamine and other NMDA antagonists: early clinical trials and possible mechanisms in depression. Am J Psychiatry. 2015;172:950–66.

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3. Czysz A, Schappi J, Rasenick M. Lateral diffusion of Gαs in the plasma membrane is decreased after chronic but not acute antidepressant treatment: role of lipid raft and non-raft membrane microdomains. Neuropsychopharmacology. 2014;40:766–73.
4. Wray N, Schappi J, Singh H, Senese N, Rasenick M. NMDAR-independent, cAMP-dependent antidepressant actions of ketamine. Mol Psychiatry. 2018. https://doi.org/10.1038/s41380-018-0083-8.
5. Singh H, Wray N, Schappi J, Rasenick M. Disruption of lipid-raft localized Gαs/tubulin complexes by antidepressants: a unique feature of HDAC6 inhibitors, SSRI and tricyclic compounds. Neuropsychopharmacology. 2018;43:1481–91.
6. Erb S, Schappi J, Rasenick M. Antidepressants accumulate in lipid rafts independent of monoamine transporters to modulate redistribution of the G protein, Gαs. J Biol Chem. 2016;291:19725–19733.