adequately drive "downstream" nodes, a second stimulating site could enhance the network disruption. Fusing the anatomic and physiologic approaches into a dynamic, network-targeted approach to closed-loop DBS may be the next horizon for personalized treatment in severe psychiatric disorders.

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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.

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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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Lipid signalling in the mesolimbic dopamine pathway

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Nutrient-sensing mechanisms provide a means whereby information about the metabolic state of the organism can be relayed to brain circuits controlling motivation. Mesolimbic dopamine (DA) neurons play a key role in mobilizing behaviour and are targeted by peripheral hormones controlling appetite and energy expenditure, such as leptin, ghrelin and GLP-1. Emerging findings suggest that neurons responding to endocrine signals can also detect fatty acids (FA). FA are essential building blocks for nerve cells but they can also have important signalling, metabolic and neuroimmune actions. Several lines of evidence implicate FA metabolism and partitioning in the brain as a nutrient sensor regulating energy homeostasis.

The type and quantity of fat consumed can be highly variable, leading to changes in the composition and amount of circulating and central FA. Dietary lipids can also affect the generation of FA synthesized and released by neural cells [1]. The biological impact of FA depends on their chemical structure. The monounsaturated FA oleate and the saturated FA palmitate are the most abundant long-chain FA in circulation and can exert different actions in the brain. Independent of changes in body weight, prolonged intake of saturated dietary fat (palm oil; enriched in palmitate) dampens mesolimbic DA function in rats while a monounsaturated high-fat diet (olive oil; containing mostly oleate) is protective [2]. Furthermore, excessive intake of saturated fat leading to obesity elicits anxiodepressive behaviour in a manner relying on neuroinflammatory responses in the nucleus accumbens (NAc) [3].

Oleate has central actions to supress feeding and neurotransmission, actions that may be mediated by cellular FA transport and metabolism. In turn, blocking FA hydrolysis from circulating triacylglycerol in the NAc has been shown to increase feeding and weight gain [4]. FA intracellular metabolism is mediated by carrier proteins including FA transporters (brain isoforms CD36, FATP1 and 4). Inside the cell FA are bound to FA binding proteins (brain isoforms FABP3, 5 and 7) that control uptake and transport of FA to different organelles. FA are activated into Acyl CoA which can be either esterified into complex lipids or oxidized by the mitochondria. DA neurons were found to express FATP1, FATP4 and FABP3, to incorporate long-chain FA and esterify FA into lipid droplets localized to the soma and processes [5]. Administration of oleate, but not palmitate, into the VTA inhibited food intake. Intra-VTA oleate also supressed the rewarding effects of sucrose and DA neuronal firing, effects prevented by blocking intracellular FA transport [5]. Therefore, DA neurons not only have the machinery for FA handling, but can alter their activity in response to FA and

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