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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metabolize and store fat. A critical goal of future research is to determine how dietary lifestyle, overconsumption and obesity development alters the DA neuron lipidome, intracellular FA metabolism and neuronal function. Indeed, human obesity is linked to increased brain FA uptake [6], a consequence which may underlie the psychiatric and neurodegenerative risks associated with obesity.

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Amyloid oligomer interactions and polymorphisms: disease-relevant distinct assembly of α-synuclein and tau

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Neurodegenerative diseases are complex diseases characterized by set of disease-specific clinical symptoms with one or more characteristic protein aggregates. However, there has been considerable overlap between multiple diseases, both in terms of clinical manifestations and protein accumulation [1]. The co-occurrence of α-synuclein and tau protein pathologies in several brain diseases implies a toxic relationship and has become an active area of research. Two of the major challenges faced in the neurodegeneration field are the formation and biological relevance of amyloid polymorphisms (strains) and the toxic interactions between amyloidogenic proteins [2]. Previously, we demonstrated that, in addition to the meta-stable oligomeric α-synuclein, tau oligomers are also present in Parkinson's disease and Dementia with Lewy bodies [3].

In our recent study, we presented novel evidence supporting the role of α-synuclein potentiating the harmful effects of tau [4]. We demonstrated that tau aggregates induced by pre-formed α-synuclein oligomers evade larger aggregate or fibril formation, thus, prolonging their oligomeric state compared to the self-aggregated tau. We evaluated the seeding propensity of tau oligomers prepared with or without pre-formed α-synuclein oligomers by exogenously adding them in three different cell models: YFP-tau expressing CV-1 cells, differentiated human neuroblastoma cell line SH-SY5Y and primary cortical neurons from embryos of Htau mouse, a transgenic tauopathy mouse model. Pre-formed α-synuclein oligomers induced tau aggregates were more potent in altering cell morphology and increasing cell death in CV-1 and SH-SY5Y cells. Moreover, these aggregates caused significant dendritic spine retraction in primary neurons when compared to the self-aggregated tau, indicating the differences in their seeding properties and toxic effects. Therefore, to gain more insight into the toxic interaction between α-synuclein and tau, we isolated complexes of oligomeric α-synuclein and tau from post-mortem Parkinson's disease (PD) brain tissues, and tau oligomers from brain tissues of progressive supranuclear palsy (PSP), a pure tauopathy without any documented α-synuclein pathology. Upon administration of these brain-derived aggregates into Htau mice, α-synuclein-tau complexes accelerated endogenous tau aggregation, caused memory deficits and spread disease pathologies as compared to pure tau oligomers.

Our study demonstrates the combined deleterious effects of α-synuclein and tau, suggesting a toxic mechanism of interaction. The ability of oligomeric α-synuclein to induce tau aggregation also points to the mechanism of cross-seeding, which has been observed among several amyloidogenic proteins, including Aβ in multiple neurodegenerative diseases [5]. This is in accordance with our previous observation, where oligomeric aggregates of Aβ, PrP, α-synuclein and TDP-43 proteins are shown to co-localize in AD pathology [6]. In conclusion, our study represents the first step to elucidate the toxic interplay between α-synuclein and tau altering the aggregation profiles and nature of amyloid deposits, possibly, resulting in the formation of unique aggregates that can cause specific loss of functions of important proteins and impairment of cellular machineries. Insights into the pathogenic interaction between α-synuclein and tau will lead to further investigation of their upstream or downstream interacting proteins that may also

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