CONFERENCIAS / KEYNOTE LECTURES

KEYNOTE LECTURE 1

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65 YEARS OF ANTIDEPRESSANTS- WHERE ARE WE NOW?

After presenting information about the Latin American Committee of the American College of Neuropsychopharmacology (ACNP), the focus of the presentation will turn to information about Major Depressive Disorder (MDD) and its treatment. The initial classes of antidepressants, MAOIs and TCAs, were developed in the 1950's. Studies of their mechanism of action revealed in the 1960's that these drugs had potent effects on synaptic transmission mediated by either norepinephrine and/or serotonin.

Based on such pharmacological effects, hypotheses of the pathogenesis of MDD were also developed in the 1960's. The 1970's and 1980's saw the development of the SSRIs such as fluoxetine or sertraline, the most commonly used drugs for MDD. In the late 1980's and 1990s, it was demonstrated that patients with recurrent depression had less chance of relapsing if maintained on antidepressants. In the 2000's, the first controlled study showing the efficacy of ketamine in treatment resistant depression (TRD) was published. Two key advances in the 2010's were the findings that the neurosteroid, brexanolone, was reasonably effective for treating postpartum depression (PPD) and confirmation that ketamine was indeed effective for TRD. Also, possible mechanisms of action of ketamine were revealed, with the most prominent idea being that its antagonism of glutamatergic NMDA receptors on GABAergic inhibitory interneurons, which resulted in enhanced glutamatergic transmission via AMPA receptors. Such observations led many groups, including our own, to search for novel compounds that produced the beneficial effects of ketamine without its rewarding properties. This led us to carrying out experiments indicating that negative allosteric modulators (NAMs) of α5-GABAA receptors, might have such properties.

KEYNOTE LECTURE 2

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BRAIN CIRCUITS FOR REGULATING EMOTION

The ability to learn about threats through social observation (observational fear learning, OFL) enables animals to learn about danger while minimizing risk of injury. Abnormal OFL resulting from social deficits or exposure to psychological trauma can produce aberrant reactions to threat and cause psychiatric disorders. However, the neural circuit mechanisms whereby threats are learned through observation, distinguished from directly-experienced threats and processed to generate appropriate behavioural responses remain poorly understood. Here we show that the dorsomedial prefrontal cortex (dmPFC) is a critical locus for OFL in mice and, using cellular resolution microendoscopic calcium imaging, show that dmPFC neurons code threat detected from observing another's behaviour in a manner distinct from direct experience of that threat. We also find that dmPFC neurons compute switches between passive and active defensive states elicited by an observationally-learned threat cue. Combining neuronal circuit mapping, calcium imaging, neuronal recordings, and optogenetics we show that a dmPFC projection to the midbrain periaqueductal grey (PAG) promotes movement during OFL, while amygdalar and hippocampal inputs to dmPFC respectively promote and constrain observer freezing. Together our findings show how the dmPFC instantiates OFL and operates as a hub coordinating long-range neural circuits to direct behavioural strategies to socially learned threats.