シグナル伝達医学講演会／大学院特別講義

“Neurobiology of stress, depression, and antidepressants: remodeling synaptic connections”

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Repeated stress exposure causes atrophy of neurons, including reduced dendrite complexity and spine density in rodent prefrontal cortex (PFC) and hippocampus, effects that could contribute to reduced volume and function of these regions in depressed patients. Recent studies demonstrate that rapid acting antidepressants, notably the NMDA receptor antagonist ketamine, produces rapid (within hours) antidepressant effects in treatment resistant depressed patients, addressing a major limitation of currently available agents (i.e. delayed onset of action and low response rates). A role for synaptic connectivity is supported by studies from Dr. Duman’s laboratory demonstrating that ketamine causes a rapid increase in the number and function of synapses in the PFC via activity dependent release of brain derived neurotrophic factor (BDNF), stimulation of the mechanistic target of rapamycin complex 1 (mTORC1), and increased synthesis of synaptic proteins. These effects of ketamine rapidly reverse the atrophy of PFC neurons caused by chronic stress and underlie rapid behavioral responses in models of depression. Further studies show that the atrophy of neurons caused by stress occurs via inhibition of mTORC1 signaling and decreased synapse number. Despite these advances the cellular trigger underlying the actions of ketamine have not been determined. Dr. Duman will discuss studies to selectively knockdown NMDA receptors on GABA vs. glutamate neurons to determine if ketamine acts via a disinhibition mechanism whereby blockade of NMDA receptors on tonic firing GABAergic interneurons leads to increased glutamate transmission and activity dependent synaptic and antidepressant behavioral responses. The signaling mechanisms and cellular trigger for other rapid acting antidepressants, including the metabolite (2R,6R)-hydroxynorketamine, Rapastinel, and scopolamine, will also be discussed. The ability of ketamine to produce rapid and long-lasting antidepressant actions highlights a major breakthrough for the treatment of depression, and characterization of the underlying mechanisms will lead to more efficacious rapid acting agents with fewer side effects.

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