（共催）

第331回 大阪大学神経科学懇話会
第2回子どものこころの分子統御機構研究センター
平成27年度連続セミナー

日時：平成27年7月1日（水）17：30～
場所：医学部臨床棟　３階　セミナー室

演題Ⅰ：*Reinforcement, Dopamine and ADHD*

Prof. Gail Tripp
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Attention deficit hyperactivity disorder (ADHD) is the diagnosis given to children and adults demonstrating persistent and developmentally inappropriate levels of inattention, hyperactivity and impulsivity that impair daily functioning. The disorder is common, affecting 5.9-7.1% of children and 5% of adults. While assumed to be neurobiological in origin, the precise etiology and pathophysiology of ADHD remains uncertain. Several researchers have proposed that individuals with ADHD have an altered sensitivity to positive reinforcement that contributes to symptoms of ADHD. Using signal detection methodology we have demonstrated that children with ADHD show: (1) increased sensitivity to individual instances of reward; (2) a stronger preference for immediate over delayed reward, a finding replicated with the spontaneously hypertensive rat (SHR), an established animal model of ADHD; and (3) reduced sensitivity to changing reward contingencies, compared to typically developing children. Drawing on the extensive evidence linking dopamine cell activity to positive reinforcement, we formulated the dopamine transfer deficit (DTD) hypothesis as a neurobiological explanation for such altered processing of positive reinforcement (Tripp & Wickens, 2008). Specifically we hypothesize that the transfer of dopamine release from reward delivery to reward-predicting cues, observed in animal studies, may be deficient in ADHD. Disruption of this anticipatory dopamine signal would result in an abnormal sensitivity to delayed or discontinuous reinforcement and increase the salience of individual instances of reward, leading to symptoms of ADHD. The results of a recent fMRI study provide preliminary support for the DTD hypothesis. Striatal responses to reward-predicting cues and reward delivery were assessed in a classical conditioning paradigm. During reward anticipation, increased blood-oxygen-level-dependent (BOLD) responses were observed in the right ventral and left dorsal striatum of controls, but not those with ADHD. The opposite pattern was observed in response to reward delivery; the ADHD group demonstrated significantly greater BOLD responses in the ventral striatum bilaterally and the left dorsal striatum relative to controls. The implications of altered reward processing and the DTD hypothesis for understanding and managing ADHD are discussed.

演題Ⅱ：*Neural mechanisms for reinforcement learning in the striatum*

Prof. Jeff Wickens
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Positive reinforcement is a controlling factor in the acquisition of learnt behaviours. Many pieces of evidence indicate that dopamine mediates the effects of positive reinforcement and that the striatum of the basal ganglia is a crucial substrate for dopamine's actions in reinforcement learning. The striatum is the input nucleus of the basal ganglia, and links sensory, cognitive, and motor information from the cerebral cortex and thalamus with reward signals transmitted by midbrain dopamine neurons. Dopamine-dependent plasticity in the corticostriatal synapses connecting the cerebral cortex to the striatum may play a key role in reinforcement learning by translating the dopamine signal into changes in synaptic efficacy. We previously showed that corticostriatal synapses exhibit dopamine dependent plasticity according to a "three factor rule" for synaptic modification. In particular, a conjunction of presynaptic cortical input and postsynaptic striatal output results in long-term potentiation when associated with dopamine inputs, but long-term depression in the absence of dopamine. Thus, dopamine may facilitate selection of particular pathways among the matrix of corticostriatal input-output possibilities. However, the striatal output neurons differentially express dopamine D1 or D2 receptors and it is important to ask how the rules for synaptic plasticity differ between D1 and D2 cells. Moreover, the precise timing of input activity is important in synaptic plasticity and may play a role in the selection of specific synapses for modification. In particular, timing of the dopamine signal may be crucial for plasticity. Therefore, the biophysical mechanisms that integrate synaptic activity at the level of individual dendritic spines on striatal projection neurons, and the modulation of these mechanisms by dopamine requires further study. I will report ongoing research into these questions and how these different aspects are integrated into mechanisms for learning. The implications of these mechanisms for treating diseases in which dopamine function is altered, such as Parkinson's disease and attention-deficit hyperactivity disorder, will be discussed.

※本講演は、医科学修士課程系別セミナーとして単位が認定されます。

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