| 강연 제목<br>Subject | Neuropsychopharmacology of Goal-Directed and Habitual Drug-Seeking Behaviors | | |
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내용 요약 (Abstract)

The ability to coordinate goal-directed and habitual controls in changing desirability of the outcome can determine flexible and effective decision-making. Goal-directed and habitual controls are distinctly governed by different cortico-basal ganglia networks harboring dorsomedial and dorsolateral striatum (DMS and DLS), respectively. Habit is an adaptive behavior driven by repeated a process of trial-and-error, but conflicts with goal-directed controls can develop maladaptive mental disorders including obsessive-compulsive disorder, substance use disorder, and alcohol use disorder (AUD). However, it is not well elucidated how astrocyte-neuron interplay through adenosine signaling regulate goal-directed and habitual reward-seeking behaviors. First, we investigated the difference between the natural reward (sucrose) and ethanol reward. Interestingly, these two rewards distinguishably developed goal-directed and habitual reward-seeking behaviors under the same operant schedule. Moreover, upon conditioning with the ethanol-containing reward, mice that initially only preferred sucrose solution not ethanol showed a stronger preference for ethanol. Additionally, the activation of adenosine 2A receptor ($A_{2A}R$) dampened this increase in the preference for ethanol. Then, we investigated whether the manipulation of the DMS-external globus pallidus (GPe) indirect medium spiny neurons (iMSNs) circuit alters the ethanol-seeking behaviors using the combination of pharmacologic and optogenetic approaches. DMS $A_{2A}R$ activation dampened operant ethanol-containing reward-seeking, whereas $A_{2A}R$ antagonist abolished the effects of the $A_{2A}R$ agonist and normalized ethanol-containing reward-seeking. Moreover, pre-ethanol exposure potentiated $A_{2A}R$-dependent reward-seeking. Interestingly, mice exhibiting ethanol-containing reward-seeking showed the reduction of the DMS iMSNs activity, suggesting that disinhibiting iMSNs decreases reward-seeking behaviors. In addition, we found that $A_{2A}R$ activation reversed iMSNs neural activity in the DMS. Similarly, optogenetic stimulation of the DMS-GPe iMSNs reduced ethanol-seeking, whereas optogenetic inhibition of the DMS-GPe iMSNs reversed this change. Next, we investigated whether the astrocytic manipulation in the DMS contributes to the flexibility of reward-seeking behaviors using the chemogenetic approach. Chemogenetic activation of the DMS astrocytes increased adenosine

level and iMSNs activities; however, the inhibition of adenosine transporter reduced chemogenetic activation-evoked synaptic events. Interestingly, chemogenetic activation of the DMS astrocytes shifted from habitual to goal-directed seeking behaviors depending on the adenosine transporter expression. Taken together, our study demonstrates that adenosine signaling-dependent astrocyte-neuron interplay in the DMS regulate reward-seeking behaviors.