Molecular Physiology

New potential mechanism of reward

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Motivation is the heart of how brain constantly making decisions and at the heart of motivation are reward and aversion. Reward also plays a vital role in emotions like fear and anxiety, as well as pathological mental process like addiction and depression. In neuroscience, reward refers to a stimulus that promote the probability or rate of which a behavior occurs induced by the stimulus.

The Mesolimbic System is composed with projections of midbrain dopamine neurons of the ventral tegmental area (VTA) to the striatum, prefrontal cortex, amygdala, hippocampus, and many other structures of the limbic system.[1,2,3] Anatomically and evolutionarily, the system exists between the neo-cortex, which is responsible for superior functions, and the brainstem, which maintains survival. Correspondingly, this system mediates physiological and cognitive processing of emotion, reward and substance abuse, thus it is considered ruling instinct but subordinate to consciousness.

Prefrontal cortex (PFC) plays a broad role in multiple stages of value-based decision-making.[4] Prefrontal area receive signals from midbrain dopaminergic neurons and project them to the striatum. Together, this network of prefrontal and subcortical areas comprises the core of the brain’s reward network.[5] The reward sensitive processes are instantiated in three key parts of the PFC, the dorsal anterior cingulate cortex (dACC), ventromedial prefrontal cortex (vmPFC) and orbitofrontal cortex (OFC).

Anterior cingulate cortex (ACC) is another related region. Due to its unique location between the mesolimbic system and prefrontal cortex, ACC is seen as the integration of emotion and cognition. There have been several reports mentioning the role of the ACC between the cortex and the midbrain, for example, the orbitofrontal cortex sends inputs to ACC about the expected value of stimuli, then the ACC in combination with the midcingulate motor area translates expectations into behaviors.[6,7,8] However, more research on ACC has focused on learning[9], decision-making[10] and the negative emotion adjustment[11]. Up to now, only little studies show its function in variability of rewards.

The cingulate cortex lies in the medial wall of each cerebral hemisphere, above and adjacent to the corpus callosum, in which ACC is the largest region, occupying third of the cingulate cortex.[12] Neural projection tracking reveals that in non-human primates ACC has broadly connections to emotion (amygdala), autonomic (lateral hypothalamus, brainstem centers), memory (hippocampal region), and reward (orbitofrontal cortex, ventral striatum) , 11 regions in total.[8,12] The function was also confirmed by fMRI imaging.[13,14] As mentioned above, since ACC has rich functions and projections, the coding of how ACC coding reward process is not clear.

The value of rewards is variable and the variability encompasses both the degree and manner. The persistent acquisition of a specific reward would decrease its value, The phenomenon is called Sensory-Specific Satiety.[15] There are also behaviors that becomes rewards in specific situations, such as water becoming a reward only when thirsty.

Existing research confirms the function of the ACC in the regulation of reward, but limited by research methods reseachers obtain different or even contradictory conclusions. Some researchers have observed that reward activates ACC neurons[16,17], others have found inhibits.[6,18,19] In Yuan's study, ACC vertebral neurons showed heterogeneity. There are some inhibited neurons less inhibited in ACC during repetitive reward acquisition. Using neuron retro-tracing techniques, the researchers point out they are pyramidal neurons projecting to the basolateral amygdala (BLA). Through Chemogenetics and In vivo Fiber photometry, Yuan et al. demonstrated that BLA-projecting ACC neurons reduce reward valuation by decreasing the number and average inhibited intensity. The above work demonstrates that excitability of BLA-projecting ACC neurons negatively regulates reward devaluation. This theory explains the adaptively control of reward intake, thereby reveals the reason why reward behavior doesn't go on unlimitedly.

All ACC-related neural circuit from emotion to reward so far are Fragmented; therefore, the links among brain regions are intriguing. In this study, the reward-value-motivation-decision-behavior chain was improved, but the interactions between the components were still crippled. Regardless, the behavioral relevance argues that BLA-projecting ACC neurons are likely important for reward and decision-making. The proportion of BLA-projecting neurons in the ACC neuron seem not to coincide with the proportion of neurons with diminished inhibition in the devaluation, suggesting there are still other circuits to be explored in the reward devaluation, perhaps other in vivo roles that are as yet to be discovered.

Depression is a broad category that encompasses the antecedent and the acquired, the physical and the social, the temporary and the persistent. In this study, the depressive-like behavior of chronic restraint stress (CRS) mice was alleviated or exacerbated by modulation of BLA-projecting ACC neurons. The finding may suggest the mechanism of depression influenced by social environment and a new anti-depression target in ACC.

In pre-experiments, shock induces ACC over-activated. Considering that inhibitory leads to a reward devaluation, over-activity may amplify reward. It leading to two possibilities, if proven.One is that social pressure prevents the process of reward devaluation, leading to addictive-like behaviors such as over-consumption when depressed or gluttony before deadline. Another possibility implies a mistake in value judgment because of subjective value deviations, just like the drawbridge phenomenon describes. This all becomes a physiological reference for social psychology.

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