Striatal acetylcholine enables behavioral flexibility

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Received: October 26, 2016
Published online: December 21, 2016

Acetylcholine is a major neurotransmitter in the brain. Among a broad range of cholinergic functions in the brain, a potential role of cholinergic system is to regulate behavioral flexibility - the ability to adapt to changes in rules governing our action. A previous study showed that systemic administration of cholinergic antagonist impairs a flexible switch of action strategy \[^{[1]}\]. However, regional contributions to cognitive flexibility remain to be clarified. One possibly important region is the striatum, in which the highest level of cholinergic markers is evident \[^{[2-6]}\].

Many pieces of evidence suggest the involvement of the striatum in behavioral flexibility. One behavioral paradigm testing this function is a set-shifting task, which has been used for several species including humans, monkeys and rodents \[^{[7-9]}\]. Indeed, previous studies showed a causal role of the dorsomedial striatum \[^{[10, 11]}\] or ventral striatum in set-shifting \[^{[12]}\]. Based on those findings, a next step to deepen our understanding on neural mechanisms enabling behavioral flexibility could be to investigate a specific role of neurochemically defined neurons such as striatal cholinergic...
interneurons.

Striatal cholinergic interneurons are localized within the striatum and mediate local acetylcholine release [13]. Several studies have shown that striatal cholinergic interneurons contribute to behavioral flexibility, based on indirectly manipulating cholinergic activity in the striatum [14-16]. To test the hypothesis that striatal cholinergic interneurons play a specific role in behavioral flexibility, we used a recently developed immunotoxin to directly and selectively target cholinergic neurons, and examined the effect on measures of behavioral flexibility.

We here highlight our recent findings of the role of striatal cholinergic system in a flexible switch of action strategy when facing a change of behavioral rules [17]. To investigate the hypothesis that cholinergic interneurons are involved in flexible switching of responses to directional cues, we prepared three different experimental conditions based on a previously described set-shifting task [8]. All of the conditions required a change between two behavioral strategies, in which an attentional shift to different stimulus dimensions was needed. Animals could obtain a food reward by choosing either a left or a right lever in an operant box in all the conditions. Initially, they had to acquire a “response strategy” in which a reward was given when they made correct responses on one side (left or right lever). Subsequently, after a shift of set, animals encountered a change in rules governing their choice strategy. After the change they had to learn a “visual cue strategy” in which a reward was provided when they made correct responses based on a light cue that indicated the correct lever.

The three conditions required attention to different stimulus dimensions after a change in rule. In the first condition, no light was presented initially, but after the change in rule a light cue indicated the correct lever. Thus, animals had to respond to a previously absent but now novel light cue for a successful shift. In the second condition, a light stimulus was always illuminated above the correct lever initially, and this remained relevant in the next visual cue learning. There, the visual cue had been relevant initially but not necessarily used for making a choice in the initial response strategy, so that after the change in rule animals needed to pay attention to a historically relevant cue. In the third condition, a light cue was randomly presented above either a left or right lever in the initial learning, in which animals had to ignore the light cue for making a correct response. Subsequently, in visual cue learning, animals had to attend to the light cue that had been previously irrelevant.

Cholinergic interneurons were selectively eliminated by local injections of immunotoxin targeting the specific neurons in either dorsomedial or ventral striatum. Two lesion groups were compared to a control group in which saline was injected. Initial learning of the response strategy remained intact across conditions and treatment types despite the lesion, suggesting that the striatal cholinergic interneurons are unnecessary for initial discrimination. On the other hand, after the set-shift in which animals faced a change in rules governing their choice, either lesion made animals perseverative to a previously correct but now incorrect response strategy. They also showed less exploratory behavior for finding out a new rule.

Importantly, cholinergic lesions in the dorsomedial striatum impaired a set-shift in which attention to the previously irrelevant cue was required. On the other hand, ventral cholinergic ablation had an effect on a shift in which a novel stimulus was introduced as a new directional cue. Neither lesion influenced a set-shift when the light cue was previously relevant. Our findings imply that striatal cholinergic interneurons play a specific role upon a change of behavioral rules, namely inhibiting the use of an old strategy and facilitating exploration of a new rule. These findings also indicate that both dorsomedial and ventral striatal cholinergic systems play this role, but their contribution is apparent in different contexts.

How can we explain an increase of perseverative responses after cholinergic loss, in which animals stick to using a previously correct but now invalid strategy? A possible idea is that cholinergic interneurons suppress an old strategy by inhibiting cortical inputs to striatal projection neurons. Indeed, Ding et al. reported that burst firing of cholinergic interneurons transiently suppresses cortical drive to striatal projection neurons [18], and they proposed it as a possible mechanism for shift of attention and redirection of behavior. Thus, burst firing of cholinergic interneurons, implying an increased acetylcholine release, may suppress a previously correct but now invalid response strategy, and then enable exploration for an alternative choice. An absence of this mechanism could account for the increase in the number of perseverative responses after a set-shift, and the associated impairment of exploratory behavior in rats with cholinergic ablation.

We now have an option to use a transgenic rat line for cholinergic system [19]. Thus, future studies using optogenetics and DREADDs (Designer Receptors Exclusively Activated by Designer Drugs) will allow more detailed investigation of the role of cholinergic interneurons. For example, those applications will make it possible to differentiate their contributions between learning and execution of a shift, and to isolate the critical time epochs in choice behavior. This will allow us to obtain more profound
understanding of the causal role of the striatal cholinergic system.

Conflicting interests

All the authors have nothing to disclose.

Acknowledgements

This study was supported by Human Frontier Science Program and the Sasakawa Scientific Research Grant from the Japan Science Society.

References