An indirect route to repetitive actions

David M. Lovinger


Commentary

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An indirect route to repetitive actions

David M. Lovinger
Laboratory for Integrative Neuroscience, National Institute on Alcohol Abuse and Alcoholism, NIH, Bethesda, Maryland, USA.

It is increasingly evident that there is a genetic contribution to autism spectrum disorders (ASDs) and other neural disorders involving excessive repetition of action sequences. Among the implicated genes in these disorders are those encoding postsynaptic scaffolding proteins with roles in synaptic transmission and plasticity. Several mouse models harboring synonymous mutations have shown alterations in synaptic transmission within the striatum, which has key roles in controlling actions and action sequences. In this issue of the JCI, Wang and coworkers show that glutamatergic synaptic transmission onto striatal projection neurons is weakened in mutant mice lacking the SH3 and multiple ankyrin repeat domains 3 (SHANK3B) scaffolding protein, defective expression of which has been implicated in ASDs. This synaptic alteration gives rise to stronger activity in the indirect pathway accompanied by decreased dendritic spines on the indirect pathway medium spiny projection neuron, indicative of decreased numbers of glutamatergic synapses. Selectively enhancing activity in this pathway reduced excessive repetitive grooming in the mutant mice. Changes in glutamatergic input to striatal projection neurons have been observed in several other murine ASD models and associated disorders. Thus, manipulation of the function of the striatal indirect pathway may be a useful therapeutic target for treating disorders characterized by excessive repetitive behaviors.

Excessive repetitive actions in autism spectrum and other disorders

Excessive repetition of actions occurs in a variety of neural disorders, including autism spectrum disorders (ASDs) and other syndromes characterized by compulsion, such as addiction (1). Thus, there is widespread interest in determining the genetic and environmental factors that contribute to excessive actions as well as the underlying circuitry. Neuroscientists have developed mouse models expressing genetic alterations in proteins that have been linked to human disorders such as ASDs (2, 3). Among these are genes that encode postsynaptic scaffolding and cell-adhesion proteins with signaling functions (4–8). Synaptic transmission and the relationship to excessive actions are subjects of intense investigation in these genetic mouse models.

In this issue, Wang and coworkers report on their examination of the mechanisms that contribute to altered transmission and plasticity at glutamatergic synapses in the striatum of mice lacking the SH3 and multiple ankyrin repeat domains 3b (SHANK3B) protein (9). Disrupted SHANK3 expression in humans has been implicated in ASDs (10, 11), and previous studies have shown that loss of this protein leads to excessive grooming in mice, one example of a repetitive/compulsive action (12–14). Moreover, Shank3-deficient mice show deficits in social interaction that mimic one component of human ASDs. Thus, understanding synapse and circuitry alterations in these mice could provide information relevant to neural dysfunctions in the human brain that underlie disorders of compulsion.

The striatum is a subcortical brain region implicated in the learning and control of actions (15). Alterations in neurons within the striatum and those that project to this brain region have been proposed to be involved in movement disorders such as Huntington’s disease and Parkinson’s disease (16). Afferent inputs from the cortex and thalamus to the striatum make glutamatergic synapses onto striatal neurons, providing excitatory input that drives the activity of these neurons (17, 18). The major targets of this excitatory drive are medium spiny neurons (MSNs) that provide output signals to other regions within the basal ganglia circuitry. The MSN efferent projections target two basal ganglia subregions. Projections to the substantia nigra pars reticulata directly inhibit this major basal ganglia output center; hence, this projection is termed the direct pathway (19). The net effect of direct pathway activation is increased activity of cortical neurons that promote action performance. The other major MSN efferent target is the globus pallidus externa segment, which inhibits basal ganglia output, with a net effect of decreased cortical activity (19). This so-called indirect pathway contributes to selection of action sequences, perhaps by inhibiting unwanted sequences following cortical activity. Imbalances in direct and indirect pathway activity have been proposed as underlying several movement disorders and are also thought to be involved in compulsive behaviors (20–22). Alterations in synaptic input to the MSNs that give rise to these pathways could produce such imbalances, and there is increasing evidence of changes at striatal synapses in mouse models of neural disorders, including ASDs (5–8).

Indirect pathway alteration in SHANK3-deficient mice

Wang and coworkers used mice expressing genetically encoded fluorescent proteins to identify direct and indirect pathway MSNs in brain slices taken from mice.
lacking the SHANK3 protein (9). Compared with those in control animals, glutamatergic synapses in Shank3-deficient mice showed decreased transmission in the indirect pathway MSNs, with no change in the synapses on direct pathway neurons. The authors also examined long-lasting changes in transmission at these glutamatergic synapses. Long-term depression (LTD) of synaptic transmission depends on activation of metabotropic glutamate receptors 1 and 5 (mGluR1 and mGluR5), L-type voltage gated calcium channels, and endocannabinoid activation of presynaptic cannabinoid 1 receptor (CB1R) (23). Wang and coworkers showed that LTD could not be induced in indirect pathway MSNs by afferent stimulation or pharmacological activation of mGluRs or calcium channels in the Shank3-deficient mice. In contrast, LTD was intact after all procedures in WT mice and in direct pathway MSNs in Shank3 mutant mice. These results support previous work indicating that LTD can be induced at glutamatergic synapses onto MSNs that give rise to both pathways (24). These changes in synaptic function were accompanied by a decrease in the number of spines on the dendrites of indirect pathway MSNs, where glutamatergic synapses are made by cortical afferents. This finding suggests that the number of glutamatergic synapses onto indirect pathway MSNs is decreased in the mutant mice and that reduction of glutamatergic synapses could be a prominent mechanism underlying the decrease in synaptic transmission onto these projection neurons.

The reduction in glutamatergic synapses and synaptic transmission onto indirect pathway MSNs decreases excitation of these neurons in response to cortical (and perhaps thalamic) activity (Figure 1). The MSNs do not depolarize sufficiently to fire action potentials in the absence of coordinated glutamatergic synaptic transmission. Thus, decreasing the strength of this transmission would result in fewer indirect pathway MSNs being activated by bouts of glutamatergic input that occur during the initiation and performance of actions. When this effect is targeted primarily to

**Figure 1. Decreased indirect pathway function in mice lacking the SHANK3 scaffolding protein.** Schematic diagrams of the cortico–basal ganglia direct and indirect pathways in WT mice and mice lacking the SHANK3 postsynaptic scaffolding protein. In WT mice, cortical synaptic input to direct and indirect pathway MSNs helps to keep the appropriate balance of striatal output that determines which actions are allowed and which are suppressed. In mice lacking Shank3, cortical input to indirect pathway MSNs is weakened, resulting in less synaptic excitation of these neurons and less GABAergic inhibitory output to the globus pallidus external segment (GPe). This results in greater GABAergic inhibition of GPe output to the substantia nigra pars reticulata (SNr), thus suppressing basal ganglia output. The net result of these circuit changes is impaired suppression of unwanted actions, excessive grooming in particular.
间接通路MSN，净效应是减少在纹状体输出到目标的，这种正常减少而不期望的移动（25）。总的来说，这个电路的变化很可能导致额外的产生某些行为。这种机制可能确实贡献到额外的量，纹状体可以减少正常行为的保持中性行为异常的。这种行为类型的研究表明缺乏SHANK3不导致到不可逆转的发展变化相关于行为功能和行为性行为，提供希望到治疗学的方法将受益于成年人。然而，处出的特定的角色作用于间接途径。这些发现表明，这种缺乏SHANK3不导致到间接途径的变化。这种变化与行为异常，同样作为在人类，将是重要的未来研究方向。

变迁在甘氨酸纹状体通路的异常行为状态的观察已经证明在一系列的神经病学，涉及异常行为和强有力的伴行为（2，3），这些发现支持了行为异常的间接途径，间接途径MSNs表达的DREADD并且在药物治疗在CNO-治疗在SHANK3-突变的动物。这种发现证明了突变的间接途径通过间接途径的异常行为状态的异常行为的。这种常见的新兴变化是的突变的影响在后突触性需求，包括SHANK3和SAPAP3（5），贡献到行为异常的行为与行为性行为的异常行为的。这将是重要的，来确定间接途径MSNs是共享目标在这些突变的动物模型。总体而言，一种药物损伤皮质兴奋性驱动到纹状体似乎是一个重要的区域，研究在ASD和其他紊乱的强迫性，可能将在未来恢复努力。

结论和未来方向

此外，SHANK3缺陷的动物模型提供另一种机制在甘氨酸传输的途径，通过在后突触性变化，被共同影响的在学习的行动（23）。因此，一个保持的缺陷在这些突触性，可能信号丢失正常的动作学习，进一步贡献到异常，行为性行为。

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通讯作者：David M. Lovinger，实验室的整合性神经科学，国家的酒精滥用和酒精的国家的健康研究所，5625 Fishers Lane，Room TS-11，Bethesda，Maryland 20892，USA。电话：301.443.2445；电子邮件：lovindav@mail.nih.gov。

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