News Release

Title

Rho kinase inhibitors ameliorate cognitive impairment in a male mouse model of methamphetamine-induced schizophrenia

Key Points

- Rho kinase
- Methamphetamine
- Schizophrenia

Summary

Schizophrenia (SCZ) is a severe psychiatric disorder characterized by positive symptoms, negative symptoms, and cognitive deficits. Current antipsychotic treatment in SCZ improves positive symptoms but hasmajor side effects and little impact on negative symptoms and cognitive impairment. The pathoetiology of SCZ remains unclear, but is known to involve small GTPase signaling. Rho kinase, an effector of small GTPase Rho, is highly expressed in the brain and plays a major role in neurite elongation and neuronal architecture. In this study, we used a touchscreen-based visual discrimination task to investigate the effects of Rho kinase inhibitors on cognitive impairment in a methamphetamine–treated male mouse model of SCZ. We found that methamphetamine activates Rho kinase in the infralimbic medial prefrontalcortex and dorsomedial striatum, which leads to cognitive impairment in male mice, and also found that Rho kinase inhibitors ameliorate methamphetamine–induced cognitive impairment, perhaps via the cortico-striatal circuit.

Research Background

Schizophrenia (SCZ) is a severe psychiatric disorder characterized by positive symptoms such as hallucinations and delusions, negative symptoms such as flat affect and social withdrawal, and cognitive deficits, with a lifetime risk of approximately 1% and a heritability of up to 80%. Current antipsychotics used to treat SCZ improve positive symptoms but also have severe side effects and only a minimal impact on negative symptoms and cognitive impairment. In addition, these drugs are only able to attenuate symptoms, and fail to delay or prevent disease progression. Thus, there are unmet needs for novel

antipsychotics with mechanisms of action that differ from those of currently available drugs.

Although the pathoetiology of SCZ remains to be determined, small GTPase signaling is known to be an SCZ-associated pathway. This signaling is activated by guanine nucleotide exchange factors and inactivated by GTPase-activating proteins (GAPs). Rho kinase is an effector of the small GTPase Rho. ARHGAP10 encodes a member of the RhoGAP superfamily of proteins that is involved in small GTPase signaling. In the central nervous system, Rho kinases play a major role in neurite elongation and neuronal architecture via phosphorylation of various downstream neuronal proteins such as myosin phosphatase-targeting subunit 1 (MYPT1) and myosin light chain 2 (MLC2).

It is important to assess whether Rho kinase inhibitors exhibit antipsychotic effects in SCZ patients who carry no mutations in ARHGAP10 and other related genes. In this regard, we have previously demonstrated that fasudil shows antipsychotic-like effects in MK-801-treated mice, a pharmacologic SCZ animal model based on the glutamate hypothesis. To further confirm this assumption, in the present study we investigated the effects of two Rho kinase inhibitors, fasudil and Y-27632, on cognitive impairment in METH-treated mice, an animal model based on the dopamine hypothesis in SCZ.

Research Results

- Intraperitoneal administration of fasudil ameliorates METH-induced cognitive deficits in the VD task
- Intraperitoneal administration of fasudil decreases METH-induced c-Fos expression in the infralimbic mPFC and DMS.
- Local injections of Y-27632 into the DMS or infralimbic mPFC ameliorate METH-induced cognitive impairment in the VD test.
- Intraperitoneal administration of fasudil decreases METH-induced p-MYPT1 (Thr696) hyperexpression in the infralimbic mPFC and DMS.
- Intraperitoneal administration of fasudil decreases METH-induced p-MLC2 (Thr18/Ser19) hyperexpression in the striatum.
- Oral administration of haloperidol and clozapine decreases METH-induced p-MYPT1 (Thr696) hyperexpression in the DMS.

Research Summary and Future Perspective

In the present study, we demonstrated that systemic i.p. treatment with fasudil dose-dependently and almost completely ameliorated METH-induced cognitive

impairment in the VD task in male mice. Local injections of the Rho kinase inhibitor Y-27632 into the infralimbic mPFC or DMS, where fasudil treatment suppressed METH-induced c-Fos expression, also attenuated METH-induced cognitive impairment. These results suggest that Rho kinase inhibitors ameliorate cognitive impairments in METH-treated mouse model of SCZ, via the action at least in the infralimbic mPFC and DMS.
To fully understand the pharmacologic and neurobehavioral features of Rho kinase inhibitors as a novel antipsychotic drug, further studies with various animal model of SCZ are required in comparison with currently used antipsychotic drugs.

Publication

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