Cognitive decline associated with schizophrenia is considered a key feature of the disease since might precede the onset of the disease and continues after psychosis, being a predictor of the disorder evolution. Current antipsychotic drugs for positive or negative symptoms have little or no effect on cognitive deficits. Furthermore, an exacerbation of cognitive deficits by some antipsychotic drugs is plausible.

Prolyl oligopeptidase (POP) is an 81-kDa monomeric serine protease that is expressed in brain and other tissues. Experimental data showed that POP inhibitors have neuroprotective, anti-aminergic and cognition-enhancing properties. In the present study, the pharmacological activity of IPR19 [(S)-1-((2S)-1-(4-(benzyloxy)-3,5-dimethoxybenzoyl)-4,4-difluoropyrrolidine-2-carbonyl) pyrrolidine-2-carbonitrile], a new potent and selective POP inhibitor, was evaluated in three schizophrenia-like mouse models based on pharmacological sub- chronic phenycyclidine (PCP) and acute dizocilpine (MK801) administration, and offspring of mothers with immune reaction during pregnancy. Behavioral responses in novel object administration, and offspring of mothers with immune reaction to chronic phencyclidine (PCP) and acute dizocilpine (MK801) schizophrenia-like mouse models based on pharmacological subchronic advances suggest that this enzyme participates in protein-protein interactions that control brain functions and cognition processes. Positive symptoms have little or no effect on cognitive deficits. Furthermore, an exacerbation of cognitive deficits by some antipsychotic drugs is plausible.

Prolyl oligopeptidase (POP) is an 81-kDa monomeric serine protease that is expressed in brain and other mammal tissues. Recent advances suggest that this enzyme participates in protein-protein interactions that control brain functions and cognition processes. Positive symptoms have little or no effect on cognitive deficits. Furthermore, an exacerbation of cognitive deficits by some antipsychotic drugs is plausible. 

The prolyl oligopeptidase inhibitor IPR19 improves cognitive deficits in schizophrenia-like mouse models

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In conclusion, the POP inhibitor IPR19 has the capacity to enhance cognitive performance in different phenotype animal models of schizophrenia, suggesting that the compound may have therapeutic potential in the cognitive deficits associated to this psychiatric disorder. The finding becomes particularly valuable as a new option of pharmacological mechanism for the treatment of cognitive dysfunctions which represent the most treatment-elusive symptoms of schizophrenia.

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Selective prolyl oligopeptidase inhibition by IPR19 as a new pharmacological treatment of the cognitive impairment associated with schizophrenia

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Prolyl oligopeptidase (POP) is an 81-kDa monomeric serine protease expressed in brain and other mammal tissues. Recent advances suggest that this enzyme participates in protein-protein interactions that control brain functions and cognition processes. Positive symptoms have little or no effect on cognitive deficits. Furthermore, an exacerbation of cognitive deficits by some antipsychotic drugs is plausible.

The effect was reversed by acute IPR19 in PCP and poly(I:C) models but not in MK801 model. In eight-arm radial maze test, PCP, MK801 and poly(I:C) models displayed fewer correct choices than controls. The effect was reversed by acute IPR19 in PCP and poly(I:C) models by samples size calculations and ranged from 6 to 23 animals per group.

In NOR test, MK801-treated animals and offspring of poly(I:C)-treated mothers showed a lower ratio of time devoted to the novel object than controls. IPR19 reversed the effect, restoring basal values. In T-maze test at 10 s and/or 40 s delay, PCP-, MK801 and poly(I:C) models displayed fewer correct choices than controls. The activity of IPR19 over other proteases of the S9 family, such as the Fibroblast activation protein (FAP) and the Dipeptidyl peptidase (DPP-IV), was very low. IPR19 selectivity was also explored through a broad panel (>50) of human receptors, ion channels, and transporters. At 10 microM, IPR19 did not show significant binding to the alternative targets explored, thus revealing the exquisite selectivity of this compound for POP. In addition to potency and selectivity, the IPR19 showed high proteolytic stability; its half-life in CD-1 mouse blood was above 120 min, while it registered 45 min in liver mouse microsomes, and over 24 h in...
human serum. Regarding the in vitro permeability of blood-brain barrier (BBB) models, IPR19 showed a logP of 2.2, 13.6±0.2% of transport in the BBB-PAMPA assay, and 25±2% in the Caco-2 permeability model. For the latter, the (A)/(B)-(B-A) ratio was 0.72, which indicates that IPR19 is not a P glycoprotein substrate.

In vivo data showed that after acute IPR19 i.p. administration (5 mg/kg) in mice, the AUC/brain ratio was 0.21. This value indicates a notable permeability of the compound across the BBB. Once in the brain tissue, IPR19 inhibited POP activity. Thus, a single i.p. dose of IPR19 (5 mg/kg) decreased ex-vivo POP activity to 45±7%, which was obtained at 6h after administration of compound. POP activity returned to basal values 12h after the injection (93±14%). This long inhibition period is related to the intrinsic nature of IPR19, which has a nitrile group that reacts with the hydroxyl moiety of Ser554 of POP to make an imidate. Neither cytotoxicity (MTT assays) nor genotoxicity (AMES and zebra fish assays) was observed for IPR19.

In conclusion, IPR19 is a potent, selective, BBB-permeable and non-toxic POP inhibitor that shows potential for the treatment of the cognitive impairment associated with schizophrenia. The mode of action of IPR19 differs greatly from other classical mechanisms, thus opening a new door for an unmet clinical need.

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