DELAYED TREATMENTS WITH A NOVEL DIKETOPIPERAZINE IMPROVES LONG-TERM MOTOR FUNCTION AFTER 6-OHDA LESION IN RATS

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Background: The current studies examined both the protective and neurotrophic actions of cyclo-L-glycyl-L-2-allylproline (cG-2allylP), a diketopiperazine, on neurochemical and behavioural changes in a rat model of Parkinson's disease.

Experiments: To examine its protective effect, either cG-2allylP (20ng/day) or saline was given intracerebroventricularly for 3 days starting 2 hours after 6-OHDA induced unilateral striatal lesion. In a subsequent experiment either cG-2allylP (0.2, 1 and 5mg/day, subcutaneously) or saline was administered daily for 14 days starting 2 weeks after the lesion. Behavioural and neurochemical outcomes were examined using the adjusting step test and immunohistochemical staining.

Results: Cyclic-G-2allylP given 2 hours after the lesion reduced the degree of motor deficit compared with the saline-treated group (p< 0.05). Delayed treatment with cG-2allylP, which was initiated after the onset of motor deficit, significantly improved motor function from week 7 onward compared with the saline-treated group (p< 0.01, p< 0.001). Neither treatment regime altered nigrostriatal dopamine depletion. The 6-OHDA lesion did not alter the Calbindin positive neurons of the striatum and Enkephaline density in the external globus palidus and the striatum. Cyclic G-2allylP treatment significantly enhanced the expression of doublecortin positive neuroblasts, but not cell proliferation in the subventricular zone (p< 0.05).

Conclusion: These studies reveal that early treatment with cG-2allylP protected against the motor deficit induced by 6-OHDA and that treatment initiated after the establishment of motor impairment significantly improved long-term motor function. These effects of cG-2allylP on functional recovery were independent of dopamine depletion. The treatment effects also appeared not to be symptomatic as the improved motor function was long-lasting.