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Inhibition of ornithine decarboxylase by ifenprodil

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Abstract

Ifenprodil (NMDA receptor antagonist) was tested as an inhibitor of ornithine decarboxylase. It was found that ifenprodil inhibited ornithine decarboxylase activity with the same potency as α-difluoromethylornithine, a major inhibitor of ornithine decarboxylase. This result suggests that ifenprodil could target either the polyamine site on the NMDA receptor complex or/and polyamine biosynthesis.

Keywords: Ifenprodil; Ornithine decarboxylase; α-Difluoromethylornithine

Excitatory amino acids are thought to be important neurotransmitters in the central nervous system. Among the four categories of receptors for these putative transmitters, the NMDA receptor has been extensively studied, mainly because specific antagonists were available. Ifenprodil has been intensively studied, as it is widely described as a non-competitive antagonist of NMDA (Ohta et al., 1993).

Recent studies indicate that the NMDA receptor is part of a complex that contains distinct recognition sites for various ligands including NMDA, glycine, ion channel blockers (MK 801-(+)-5-methyl-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5,10-imine) and polyamines (Williams et al., 1991). This suggests that polyamines (which are also involved in cell proliferation and differentiation) may also participate in excitatory synaptic transmission. Large increases in the activities of two enzymes of polyamine biosynthesis (ornithine decarboxylase and *S*-adenosylmethionine decarboxylase) are reported in the reperfusion phase following global ischemia. The increase in polyamine metabolism is suggested to be one of the factors contributing to the involvement of the NMDA receptor in ischemia-related cytotoxicity.

The ability of ifenprodil to potently antagonise the modulating effects of spermidine on the NMDA receptor probably explains the cytoprotective effects of this polyamine. It is thus suggested that ifenprodil exerts its activity through antagonism of the polyamine modulatory site of the NMDA receptor complex (Carter et al., 1989).

In spite of the close relationship between the activity of ifenprodil and the polyamine, no studies have been done to explain the mode of action of ifenprodil through an enzymatic mechanism. In order to study the effect of ifenprodil on polyamine biosynthesis, its capacity to inhibit ornithine decarboxylase activity was investigated and compared to that of a reference irreversible inhibitor of this enzyme (α-difluoromethylornithine). The activity of N^1N^4-bis(benzyl)-N^1N^4-bis(methyl)-putrescine (BMeBBPu), a new polyamine analogue, was also determined.

The ornithine decarboxylase was from *E. coli*. The test was performed by preincubating (15 min) ornithine decarboxylase with 5 mM of ifenprodil, α-difluoromethylornithine or BMeBBPu. Then 5 mM of ornithine was added and further incubated (60 min). The reaction was ended by the addition of perchloric acid (6% v/v) and putrescine was then quantitated by a high performance liquid chromatography assay as benzoyl-putrescine (Schenkel et al., 1995). The results are the average of 3 separate experiments.

The results (Table 1) show an inhibitory effect with all the tested compounds, the most active compound being the BMeBBPu derivative, which caused 50% of inhibition. α-Difluoromethylornithine and ifenprodil exhibited nearly the same inhibition (32%).

Among the approximately thousand papers related to ifenprodil, not one has studied the enzymatic activity of this compound. The finding of its effect on ornithine

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Table 1
Activity of ornithine decarboxylase on 5 mM of ornithine (control) after incubation with 5 mM of ifenprodil, α-difluoromethylornithine or BMeBBPu

Compounds tested	nmol of putrescine produced (mean (range), $n = 3$)	% of inhibition
Control	0.0340 (0.0328–0.0347)	0.0
α-Difluoromethylornithine	0.0230 (0.0221–0.0245)	32.3
Ifenprodil	0.0230 (0.0225–0.0236)	32.4
BMeBBPu	0.0168 (0.0168–0.0172)	50.7

decarboxylase could indicate that beside its action at the polyamine site on the NMDA complex receptor, ifenprodil could act by decreasing intracellular polyamine levels through inhibition of ornithine decarboxylase. Our results suggest that lipophilic polyamine analogues which inhibit ornithine decarboxylase activity (like BMeBBPu) could be good candidates to target the central nervous system and contribute to the search for new drugs against nervous diseases such as Alzheimer's disease.

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