MONO-ACYLATED SPERMINES: ANTAGONISTS OF GLUTAMATE RECEPTORS

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Antagonism of L-glutamate receptors by micromolar concentrations of mono-acylated spermines and other polyamines has been demonstrated on a cortical wedge preparation. These substituted polyamines were first screened using the metathoracic retractor unguis nerve-muscle of the locust Schistocerca gregaria. Antagonism of the quisqualate sensitive glutamate receptors of this preparation was inferred from the depression of the twitch contraction evoked by stimulation of the excitatory motoneurones which innervate the retractor unguis muscle.

Experiments on mammalian excitatory amino acid receptors were performed with the rat cortical wedge preparation described by Harrison and Simmonds (1985). Antagonism of the (DL)-α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) sensitive L-glutamate receptors (AMPA-GluR) was compared with that obtained in the invertebrate screen. Control responses to N-methyl-D-aspartate (NMDA) and AMPA, at 2.5 and 5.0 μM, were obtained in magnesium-free Krebs bicarbonate buffer gassed with 95% oxygen/5% carbon dioxide containing tetrodotoxin (100 nM) to suppress epileptiform discharges. Tissues were incubated with philanthotoxin-343 (PhTX-343) (10 μM) (Blagbrough et al 1989) for 20 min, washed and exposed to repeated additions of NMDA or AMPA. The amino acid responses progressively declined with successive exposures to agonist to 40% and 20% of control levels, respectively, by the third application. A similar, but less marked antagonism was seen with N-(4-hydroxyphenylpropanoyl)-spermine which significantly antagonised AMPA responses by 23%, 13%, and 19% at the third application of the agonist, following synthetic mono-acylated spermine at 1, 10, and 100 μM respectively. The analogue lacking a methylene group, N-(4-hydroxy-phenylacetyl)-spermine, was virtually inactive over a similar concentration range against AMPA. Neither of these analogues, at low concentrations (1 and 10 μM), had any effect on responses to NMDA, but significant antagonism was obtained in the presence of each of these synthetic toxins at a higher concentration (100 μM), the responses were reduced by 55% and 92% respectively with the phenylpropanoyl and phenylacetyl analogues. Following washout of the analogues, there was no recovery from the antagonism with two subsequent additions of NMDA. The antagonism of the NMDA response by the phenylacetyl analogue was not prevented by the prior addition of D-serine (1 mM). The quinoxaline DNQX (1μM) reversibly reduced AMPA responses by 51%.

Thus, antagonism of AMPA-GluR by synthetic PhTX-343 and its analogue N-(4-hydroxyphenylpropanoyl)-spermine appears to be use-dependent which contrasts with antagonism by DNQX. Antagonism of the NMDA response (Watkins and Collingridge 1989) may be due to an action at the "polyamine site" on the glutamate receptor complex (Carter et al 1989).

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