Protection against post-ischaemic neuronal loss in gerbil hippocampal CA1 by glycineB and AMPA antagonists

Short Communication

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Accepted August 5, 1997

Summary. Novel antagonists of the glycineB site of the NMDA receptor (MRZ 2/570, MRZ 2/576), and an AMPA receptor antagonist, NBQX were tested in 3-min. global ischaemia in gerbils. Untreated animals showed after 14 days a loss of almost 90% of pyramidal neurones in the CA1 region, which was prevented by NBQX, and reduced to 50% by both glycineB antagonists. NBQX produced a delayed, long lasting (up to 24 hr) hypothermia while hypothermia with both glycineB antagonists was transient.

Keywords: Forebrain ischaemia, gerbil, glycineB antagonists, MRZ 2/570, MRZ 2/576, NBQX, hippocampus.

Introduction

NMDA receptor antagonists provide clear neuroprotection in focal models of brain ischaemia (Park et al., 1988). However, in models of global/forebrain ischaemia, e.g. in Mongolian gerbils, the protective effect of the uncompetitive NMDA receptor antagonist MK-801 (Gill et al., 1988) appeared to be dependent on postischemic hypothermia (Buchan and Pulsinelli, 1990; Łazarewicz et al., 1994).

Apart from glutamate, a more prolonged, but relatively modest increase in the concentration of extracellular glycine has been observed under ischemic conditions (Globus et al., 1991). Therefore, antagonists of the glycine site of the NMDA receptor (glycineB) may offer an alternative neuroprotective approach. Unfortunately, little is known about the therapeutic potential of such compounds due to poor bioavailability of most glycineB antagonists (Wood et al., 1992). Recently, Pellegrini-Giampietro and colleagues (1994) reported that the glycineB antagonist, 7-chlorothiokynurenic acid is neuro-
Fig. 1. Effect of post-treatment with NBQX, MRZ 2/570 and MRZ 2/576 on histological damage in the CA1 area of the gerbil hippocampus 14 days after 3-min forebrain ischaemia. Results are expressed as per cent cell loss (A) or as the number of rats showing respective grading (B). *p < 0.05 vs. control. *p < 0.05 vs. NBQX (Dunnett's test).

N = 10, 14, 14 and 10 respectively

Protective in global ischaemia in gerbils. Recently a series of novel glycine$_B$ antagonists, tricyclic pyridino-phtalazindiones, which are moderately potent in vitro, but potent in vivo, has been characterised (Parsons et al., 1997).

The aim of this study was to assess the neuroprotective potential of two of these tricyclic pyrido-phtalazindione glycine$_B$ antagonists, MRZ 2/570 and MRZ 2/576 using an AMPA receptor antagonist, NBQX (2,3-dihydroxy-6-nitro-7-sulfamoyl-benzo(F)qui-noxaline), as a reference agent (Buchan et al., 1991; Frank et al., 1993; Sheardown et al., 1990).