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Rapid communication

Group I metabotropic glutamate receptors limit AMPA receptor-mediated oligodendrocyte progenitor cell death

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Abstract

Oligodendrocyte progenitor cells were found to be vulnerable to kainate excitotoxic insults, an effect inhibited by either the selective α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor antagonist (1-(4-aminophenyl)-4-methyl-7,8-methylenedioxy-5*H*-2,3-benzodiazepine (GYKI 52466)) or the selective group I metabotropic glutamate (mGlu) receptor agonist, (*S*)-3,5-dihydroxyphenylglycine. The protective effects of (*S*)-3,5-dihydroxyphenylglycine were reversed by the selective mGlu receptor antagonist, (*S*)-α-methyl-4-carboxyphenylglycine. These data suggest that group I mGlu receptors may limit oligodendrocyte progenitor cell degeneration during acute brain insults.

Keywords: Oligodendrocyte; Kainate; Glutamate receptor, metabotropic

Oligodendrocyte progenitor cells differentiate into oligodendrocytes, brain macroglia responsible for axon myelination. Cerebrocortical oligodendrocyte progenitor cells express several glutamate receptors including ionotropic α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) (GluR2–GluR4) and kainate (GluR6, GluR7, KA1 and KA2) receptor subunits, but lack functional *N*-methyl-D-aspartate (NMDA) receptors (Patneau et al., 1994). Additionally, oligodendrocyte progenitor cells are also reported to express G_q-coupled group I metabotropic glutamate (mGlu) receptors (mGlu1 and/or mGlu5 receptors) (Holzwarth et al., 1994). Emerging data suggest that mature oligodendrocytes may be susceptible to AMPA/kainate receptor-mediated excitotoxic insults (Matute et al., 1997; McDonald et al., 1998). We report here that AMPA receptor over-activation induces marked oligodendrocyte progenitor cell death, an effect inhibited via group I mGlu receptor co-activation.

Cultured oligodendrocyte progenitor cells (> 90% A_2B_5-immunoreactive) were prepared from mixed cerebrocortical glia (Holzwarth et al., 1994) and cell viability determined via fluorescein diacetate/propidium iodide fluorescence microscopy (Matute et al., 1997). Kainate ($pEC_{50} = 3.9 \pm 0.3$) elicited significant cell death, an effect abolished by the selective AMPA receptor antagonist, 1-(4-aminophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine (GYKI 52466, 50 μM) (Matute et al., 1997) (Fig. 1A). When tested alone, neither 50 μM GYKI 52466 nor 1 mM NMDA significantly influenced cell viability (data not shown).

Alone, the selective group I mGlu receptor agonist (*S*)-3,5-dihydroxyphenylglycine ((*S*)-DHPG), 100 μM) failed to influence cell viability. However, (*S*)-DHPG significantly reduced acute (6 h) kainate toxicity, an effect reversed by the selective mGlu receptor antagonist (*S*)-α-methyl-4-carboxyphenylglycine ((*S*)-MCPG, 1 mM) (Fig. 1B) (Conn and Pin, 1997). Significant (*S*)-DHPG (100 μM)-mediated protection was not observed during 24 h kainate (300 μM) exposure paradigms (data not shown).

Previous neuronal studies suggest that group I mGlu receptors may either be neuroprotective or may enhance ionotropic glutamate receptor (predominantly NMDA receptor)-mediated neurotoxicity (Nicoletti et al., 1999). The current study is the first report of group I mGlu receptors limiting AMPA receptor-mediated oligodendrocyte progenitor cell death and suggests that group I mGlu receptors

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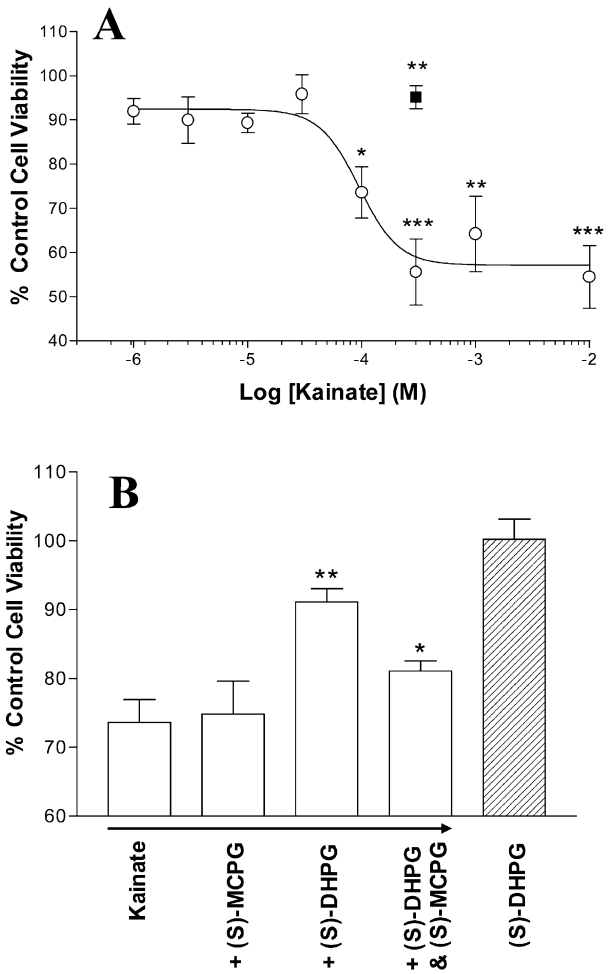

Fig. 1. (A) Kainate (○) (24 h exposure) elicits marked oligodendrocyte progenitor cell death (abolished by 50 μM GYKI 52466 (■)). (B) (*S*)-DHPG (100 μM) limits kainate (6 h, 300 μM)-evoked cell death and reversal by 1 mM (*S*)-MCPG (open bars). Alone, (*S*)-DHPG was without effect (striped bar). Data represent the mean (±S.E.M.) of at least four experiments. $^{*}P < 0.05$, $^{**}P < 0.01$ and $^{***}P < 0.001$ versus respective controls (one-way analysis of variance (Tukey–Kramer post test) or Student's two tailed paired *t*-test, where appropriate).

may act to limit white matter degeneration during acute excitotoxic insults.

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References

Conn, P.J., Pin, J.P., 1997. Pharmacology and functions of metabotropic glutamate receptors. Annu. Rev. Pharmacol. Toxicol. 37, 205–237.

Holzwarth, J.A., Gibbons, S.J., Brorson, J.R., Philipson, L.H., Miller, R.J., 1994. Glutamate receptor agonists stimulate diverse calcium responses in different types of cultured rat cortical glial cells. J. Neurosci. 14, 1879–1891.

Matute, C., Sanchez-Gomez, M.V., Martinez-Millan, L., Miledi, R., 1997. Glutamate receptor-mediated toxicity in optic nerve oligodendrocytes. Proc. Natl. Acad. Sci. U. S. A 94, 8830–8835.

McDonald, J.W., Althomsons, S.P., Hyrc, K.L., Choi, D.W., Goldberg, M.P., 1998. Oligodendrocytes from forebrain are highly vulnerable to AMPA/kainate receptor-mediated excitotoxicity. Nat. Med. 4, 291–297.

Nicoletti, F., Bruno, V., Catania, M.V., Battaglia, G., Copani, A., Barbagallo, G., Cena, V., Sanchez-Prieto, J., Spano, P.F., Pizzi, M., 1999. Group-I metabotropic glutamate receptors: hypotheses to explain their dual role in neurotoxicity and neuroprotection. Neuropharmacology 38, 1477–1484.

Patneau, D.K., Wright, P.W., Winters, C., Mayer, M.L., Gallo, V., 1994. Glial cells of the oligodendrocyte lineage express both kainate- and AMPA-preferring subtypes of glutamate receptor. Neuron 12, 357–371.