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Aspartate as a selective NMDA receptor agonist in cultured cells from the avian retina

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Abstract

Although glutamate is considered the natural neurotransmitter that mediates excitatory function in the CNS, other active natural compounds can also drive the functional activation of excitatory amino acid receptors (EAAR). L-aspartate is the most likely neurotransmitter to mimic the actions of glutamate. Here we show that L-aspartate promotes the release of GABA acting selectively on the NMDA receptor subtype. Retina cell cultures, when exposed to excitatory amino acids (EAA), release [^{3}H] GABA previously incorporated by the cells. Both L-glutamate and L- and D-aspartate at 100 μM concentration, promote the release which can be mimicked by kainate and NMDA. While aspartate-induced release of [^{3}H] GABA occurs in the presence of 1 mM Mg^{2+}, NMDA (100 μM) promotes the release only when Mg^{2+} is omitted from the superfusing medium. However, in the absence of Mg^{2+} the efficacy of l- and d-aspartate (100 μM) to activate [^{3}H] GABA release increases by a factor of 2 when compared to the release observed in the presence of 1 mM Mg^{2+}. NMDA and aspartate induced release of [^{3}H] GABA is completely inhibited by 10 μM MK-801 and is not affected by CNQX (100 μM). In the presence of Mg^{2+}, aspartate-induced release of [^{3}H] GABA is also completely inhibited by MK-801 (10 μM) and is not significantly affected by CNQX (100 μM). The [^{3}H] GABA release induced by kainate (100 μM) is fully inhibited by CNQX (100 μM) and is not affected by MK-801 (10 μM). Our results indicate that in the retina, l-aspartate modulates its excitatory function on a set of GABAergic cells via the selective activation of NMDA receptors. The fact that L- and D-aspartate (but not D-glutamate) induce the release of GABA even in the presence of Mg^{2+} suggests that the electrogenic uptake of aspartate is required to lower the affinity of the NMDA channel for Mg^{2+}. The observation that D-glutamate (200 μM), which is not taken up by the cells, activates the efflux of GABA only when Mg^{2+} is omitted from the incubating medium, supports this possibility.

Glutamate is the major excitatory neurotransmitter in the CNS and mediates its action via the activation of several subtypes of excitatory amino acid receptors. Both ionotropic and metabotropic receptors are present throughout the nervous system of most if not all species (Fonnum, 1984; Gasic and Hollman, 1992; Monaghan *et al.*, 1989; Pin and Duvoisin, 1995). In the retina, glutamate receptors have been localized in bipolar, horizontal, amacrine and ganglion cells and the activation of these receptors induces the release of several neuroactive substances including GABA (Barnstable, 1993; Hamasaki-Britto *et al.*, 1993; Miller and Slaughter, 1986). Several publications have shown that, in the retina, a substantial portion of the release of GABA induced by excitatory amino acids occurs via mechanisms independent of external calcium (Ferreira *et al.*, 1994; Do Nascimento and de Mello, 1985; Schwartz, 1987; Yazulla and Kleinschmidt, 1983), due to the reversal of the sodium coupled GABA uptake carrier, as a result of the decrease in the sodium electrochemical potential gradient (McMahon and Nicholls, 1991).

Glutamate seems not to distinguish between the various EAA receptor subtypes and displays no selectivity towards them. Therefore, EAARs can only be pharmacologically differentiated from each other with selective agonists and antagonists that specifically interact with them. Based on its agonistic properties kainic acid, AMPA and NMDA have defined with precision the existence of at least two major subtypes of ionotropic receptors that are named according to their selective response to AMPA/KA or NMDA. The same is true for metabotropic receptors that can also be pharmacologically differentiated with the use of selective ligands (Burnashev, 1993; Hollman and Heinemann, 1994; Monaghan *et al.*,

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