cGMP CONTROL OF KAINATE RECEPTOR ACTIVATION IN RAT CEREBELLAR CORTEX

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Cyclic GMP is produced at considerable extent, and roles for intracellular cGMP have been widely investigated in the cerebellum: we previously found that cGMP dependent on activation of ionotropic glutamate receptors/NO synthase/sGC pathway accumulated in Purkinje cells, consistent with the cGMP involvement in glutamatergic parallel fibre/Purkinje cell synapse plasticity. Extracellular cGMP is considered a reliable measure of cerebellar glutamatergic transmission (during microdialysis); nevertheless, roles for extracellular cGMP have been scarcely searched for. In the present paper we investigated on extracellular cGMP effects on glutamatergic terminals of parallel/climbing fibres. Briefly, purified synaptosomes prepared from adult rat cerebellum by separation on discontinuous Percoll gradient and preincubated with [^{3}H]D-aspartate were exposed to drugs in parallel superfusion chambers; [^{3}H]D-aspartate fractional release was evaluated in superfusion fractions. AMPA (10-300 μM) increased [^{3}H]D-aspartate efflux in a CNQX-sensitive way; involvement of AMPA receptors was confirmed by sensitivity to the selective AMPA receptor antagonist GYKI 52466 and insensitivity to the kainate receptor antagonist NS 102. (*S*)-CPW 399, a full AMPA receptor agonist that prevents the receptor desensitised conformation, almost equated the responses to AMPA in the presence of cyclothiazide, that increases AMPA efficacy by inhibiting receptor desensitisation. Kainate (100 μM)-evoked [^{3}H]D-aspartate release was almost completely abolished by GYKI 52466 (30μM); preincubation with concanavalin A, that prevents kainate receptor desensitization, revealed a kainate response resistant to GYKI 52466, that can be ascribed to kainate receptor activation, CNQX (10 μM)- and NS 102-sensitive. Extracellular cGMP (0.5-500 μM) impaired the kainate receptor-mediated [^{3}H]D-aspartate release, while it was ineffective against AMPA receptor-mediated, or NMDA-, 4-aminopyridine- or K^+-evoked [^{3}H]D-aspartate release. In conclusion, we found that: - release-stimulating presynaptic AMPA and kainate receptors are present on cerebellar glutamatergic nerve terminals; - extracellular cGMP selectively impairs kainate receptor-mediated responses. Extracellular cGMP was effective at concentrations compatible with the hypothesis that inhibition of kainate-evoked glutamate release from terminals of parallel/climbing fibres might be a physiologically relevant process in the cerebellum and that cGMP production related to glutamatergic transmission activation onto Purkinje cells might act as a retrograde signal to control the kainate-dependent activation of glutamate release.