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METABOTROPIC GLUTAMATE RECEPTORS MODULATE PERIAQUEDUCTAL GRAY GLICINE RELEASE: INTERACTION WITH A1 ADENOSINE RECEPTORS

Mariani L., 1° anno di corso del Dottorato di Ricerca in Scienze Farmacologiche e Fisiopatologia Respiratoria, XVII ciclo. Durata del Dottorato in anni: 4. Sede di servizio: Dpt of Experimental Medicine, Section of Pharmacology "L. Donatelli", II University of Naples.

Introduction

Glutamate is ubiquitously distributed in the CNS where it represents the main neurostransmitter at fast excitatory synapses (Nakanishi, 1994; Conn and Pin, 1997; Nakanishi et al., 1998). In the brain, neurons signaling can be modified by presynaptic glutamate receptors that directly regulate glutamate release, or by glutamate receptors localized postsynaptically on glutammatergic or non glutammatergic neurons. Glutamate binds to both ion channel-associated receptors (iGlu) and G protein coupled metabotropic glutamate (mGlu) receptors (Nakanishi, 1994; Conn and Pin, 1997; Nakanishi et al., 1998). Moreover, these receptors appear to be under control of endogenous neuromodulators, like adenosine, which influences synaptic functions and neuronal activity within local circuits, through a common tranductional pathway. In this study we investigated the effects of group I and II mGlu receptors ligands on glycine extracellular concentrations at the periaqueductal gray (PAG) level by using *in vivo* microdialysis.

Methods

Male Wistar rats were implanted with concentric probes into the PAG. The following day probes were perfused with artificial cerebrospinal fluid (ACSF) at a rate of 0.8 µl/min using a infusion pump. 12 consecutive dialysate samples were collected each 30 min . Rats received drugs directly through the dialysis probe between the fifth and the sixth dialysate sample. Dialysates were analysed for amino acids content using an HPLC methods.

Results

(S)-3,5-DHPG (1 and 5 mM), an agonist of group I mGlu receptors but not CHPG (3 and 5 mM), a selective agonist for mGlu5 receptors, was noticed to increase the dialysate glycine levels in a concentration-dependent manner (60 ± 15% and 136 ± 13%, respectively). CPCCOEt (1 mM), a selective mGlu1 receptor antagonist, perfused in combination with (S)-3,5-DHPG, counteracted the effect induced by (S)-3,5-DHPG, but did not change *per se* the extracellular PAG glycine values, even at the highest dosage used (2 mM). MPEP (1 and 2 mM), a selective antagonist of mGlu5 receptor, did not modify extracellular glycine level. 2R, 4R-ADPC (25 and 50 µM), an agonist of group II mGlu receptors, decreased the dialysate glycine in a concentration-dependent manner (-26 ± 4% and -54 ± 6%, respectively). The 2R, 4R-ADPC induced decrease in extracellular glycine was prevented by EGlu (0.5 mM), a selective group II mGlu receptors antagonist. EGlu (0.5 and 1 mM), *per se*, led to a significant decrease (-56 ± 7% and –57 ± 2%, respectively) in extracellular PAG glycine too. This effect was prevented by DPCPX (100 µM), a selective antagonist for A1 adenosine receptors. Intra-PAG perfusion of CPA (0.1-1 mM), at selective A1 adenosine receptors agonist, decreased the extracellular PAG glycine values (–47 ± 13%) at the highest dosage. Dipyridamole (100 µM), an inhibitor of both adenosine reuptake and phosphodiesterases, decreased extracellular glycine (-28 ± 7%). Extracellular concentrations of glutamine never changed throughout this study.

Conclusion

These data show opposing effects of group I and group II mGlu receptors in the regulation of PAG glycine values. Moreover, functional interaction between group II mGlu and adenosine A1 receptors, which possibly operate through a common transductional pathway, may be relevant in the physiological control of glycine release in awake, freely moving rats at the periaqueductal gray matter.

References

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