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ORIGINAL ARTICLE

Interaction Between P2X and Nicotinic Acetylcholine Receptors in Glutamate Nerve Terminals of the Rat Hippocampus

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Introduction

Nicotinic acetylcholine receptors (nAChRs [constituted by pentameric association of α2–10 and β2–4 subunits]) and P2X receptors (P2XRs [activated by ATP and constituted by multimeric association of P2X1–7 subunits]) are both ionotropic receptors permeable to cations, which have in common the disparity between the wealth of data showing their presence in the brain and little evidence of their participation in mediating synaptic transmission. This has led to the proposal that both nAChRs and P2XRs might primarily modulate rather than directly mediate synaptic transmission, which is in accordance with the predominant presynaptic localization of both receptor subtypes (Role and Berg, 1996; Cunha and Ribeiro, 2000). Interestingly, both functional neurochemical (Allgaier et al., 1995; Salgado et al., 2000; Diáz-Hernández et al., 2002) and electrophysiological studies (Barajas-Lopez et al., 1998; Searl et al., 1998; Zhou and Calligan, 1998; Khakh et al., 2000) indicated a close interaction between nAChRs and P2XRs, which is paralleled by a corelease of ATP and ACh from central terminals (e.g., Richardson and Brown, 1987). Because glutamate release in the hippocampus is controlled by both nAChRs (e.g., McGehee et al., 1995) and P2XRs (Khakh et al., 2003; Rodrigues et al., 2005), we investigated if there was a functional interaction between these two presynaptic ionotropic receptors in the control of glutamate release in the rat hippocampus.

Results

The modulation of neurotransmitter release from superfused synaptosomes allows unambiguous definition of a modulatory system being presynaptic. Using this approach, we confirmed (*see* Rodrigues et al., 2005) that the P2XR agonist, α,β-methylene ATP (60 μ*M*), enhanced glutamate release by 35.2 ± 6.0% ($n = 6$) from hippocampal nerve terminals. This effect was prevented by the P2R antagonist PPADS (20 μ*M*) (Fig. 1).

Electrophysiological recordings in rat hippocampal slices had shown previously that nAChRs also facilitated glutamatergic transmission, an effect ascribed to presynaptic receptors (e.g., McGehee et al., 1995). Accordingly, we have now observed that the nAChR agonist epibatidine (100 n*M*) facilitated glutamate release by 27.2 ± 5.3% ($n = 6$) from rat hippocampal nerve terminals (Fig. 1). This effect was prevented by the nAChR antagonist, *d*-tubocurarine (1 μ*M*) (Fig. 1). This unambiguously shows that nAChRs presynaptically facilitate the evoked release of glutamate in the hippocampus.

Because it was observed in heterologous expression systems that nAChRs and P2XRs interacted tightly (Khakh et al., 2000) and that there was a

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