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Short communication

Suppression of evoked IPSPs by arachidonic acid and prostaglandin $F_{2\alpha}$

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Abstract

Arachidonic acid (AA) and certain prostaglandins appear to antagonize $GABA_A$ receptors in synaptoneurosomes [18]. We report here that perfusing hippocampal slices with AA or prostaglandin $F_{2\alpha}$ diminishes evoked IPSP conductance and increases CA1 pyramidal cell input resistance. The effects of the two compounds were similar, though not identical, in time course, magnitude, and response to washout. These findings suggest that high levels of AA and its metabolites may bias neurons towards excitation.

Keywords: CA1; Eicosanoid; Epilepsy; Excitotoxicity; Hippocampus; Input resistance

While characteristic patterns of nerve cell loss have been described for certain epilepsies [13], the actual mechanism of cell death in these disorders remains unclear. According to the excitotoxicity hypothesis [5,10,15] seizure activity releases large quantities of excitatory amino acids (EAAs), particularly glutamate, which promote prolonged neuronal depolarization and lead to elevated intracellular calcium. Dysregulation of calcium homeostasis produces uncontrolled activation of intracellular proteases, nucleases, and lipases leading to cell injury and, eventually, cell death.

Arachidonic acid (AA) and its metabolites are, like calcium, normal signalling molecules which can produce pathological changes at high concentrations [11,16,19]. Seizures, head trauma, hypoglycemia, and ischemia elevate intracerebral levels of eicosanoids (AA, prostaglandins, thromboxanes, and leukotrienes) [1,14,18,20]. NMDA receptor-mediated calcium influx, thought to be integral to some forms of excitotoxicity [5,10], activates PLA_2 which splits AA out of the plasma membrane [17,18,21]. Metabolism of AA produces vasoactive compounds (e.g. LTC_4) which may alter cerebrovascular resistance and permeability leading to vasogenic edema [2]. Furthermore, AA breakdown by cyclooxygenase, lipoxygenase, or microsomal cytochrome P_{450} produces oxygen free radicals which can cause lipid peroxidation, protein denaturation, and DNA damage [12,21].

Another role for eicosanoids in excitotoxicity is suggested by the recent finding that AA and certain prostaglandins antagonize muscimol-induced Cl^- flux into synaptoneurosomes, presumably by blocking $GABA_A$ receptors [18]. Blockade of $GABA_A$ receptors during episodes of hyperexcitability would exacerbate excitotoxic effects and promote continued synaptic bombardment. We set out to determine the effect of exogenous eicosanoids on inhibition in a partially intact neural system: the hippocampal slice. We found that, in hippocampal pyramidal cells, AA and prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) application significantly suppressed evoked IPSP conductance and increased input resistance.

Female Sprague–Dawley rats (150–250 g) were sacrificed by decapitation and the brain removed, cooled with ice cold oxygenated artificial cerebrospinal fluid (ACSF: NaCl 124 mM, $NaHCO_3$ 26 mM, NaH_2PO_4 1.25 mM, KCl 3 mM, $MgSO_4$ 2.0 mM, $CaCl_2$ 2 mM, and glucose 10 mM), blocked, and glued to a vibratome stage with cyanoacrylate. Horizontal hippocampal slices were cut at 400 μm and submerged in oxygenated room temperature ACSF until needed for recording.

Slices were placed in a low volume submersion chamber, held under a fine gold wire mesh, and perfused (2.5 ml/min) with 29–31°C oxygenated ACSF. Sharp glass electrodes (60–110 MΩ) filled with 4 M potassium acetate were lowered into the CA1 pyramidal cell layer. The

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