Effects of Soman-Induced Convulsions on Phosphoinositide Metabolism†

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ABSTRACT

Turnover of [3H]phosphoinositides (PI) was examined in brain slices from the hippocampus of rats undergoing soman-induced seizure activity. Hydrolysis of PI was determined by measuring the accumulation of [3H]inositol-1-phosphate (IP₁). Incubation of hippocampal slices in the presence of carbachol or norepinephrine (NE) increased PI hydrolysis. Stimulated hydrolysis by NE, but not carbachol was significantly reduced in slices from soman-challenged rats undergoing convulsive activity. NE-stimulated PI hydrolysis was not reduced in slices from animals exposed to soman that did not exhibit convulsive activity. In rats surviving for 24 h, the response to NE was not different from control rats. In control slices, NE-stimulated hydrolysis of PI was potentiated by GABA. No potentiation by GABA was seen in slices from animals undergoing seizures. Uptake and incorporation of myo-[2-3H]inositol into phospholipids was reduced in slices from rats undergoing convulsions. Reduced IP₁ production appeared to be owing, in part, to decreased synthesis of inositol

†The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as the views of the Army or the Department of Defense.

In conducting the research described in this report, the investigators adhered to the “Guide for the Care and Use of Laboratory Animals” as adopted and promulgated by the National Institutes of Health publication 86-23.

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lipids. These observations suggest that during soman-induced seizure activity, there is an apparent decrease in the response of the PI second messenger system to NE stimulation, and that this may contribute to the severity and duration of convulsions and brain damage resulting from exposure to soman and other anticholinesterase compounds.

**Index Entries:** Soman; hippocampus; convulsions; seizures; phosphoinositides; inositol norepinephrine; carbachol; GABA.

**INTRODUCTION**

In high doses, soman (methylpinacolylphosphonofluoridate) and other acetylcholinesterase (AChE) inhibitors induce seizure activity in humans (McLeod, 1985) and laboratory animals (Wills, 1963). As a consequence, exposure to anti-AChE compounds may cause seizure-related brain damage (SRBD) (Lemercier et al., 1983; McDonough et al., 1987; Ballough et al., 1995). High levels of unhydrolyzed acetylcholine (ACh) produce persistent stimulation of cholinergic receptors and initiation of convulsions or seizures (Lipp, 1968; McDonough et al., 1987; Shih et al., 1990; McDonough and Shih, 1993).

As a result of the accumulation of unhydrolyzed ACh, an increase in the discharge rate of locus ceruleus (LC) neurons and massive release of norepinephrine (NE) from the LC terminals have been observed in soman-challenged rats by Shipley et al. (1990), Ennis and Shipley (1992), and El-Etri et al. (1992, 1993). Adrenergic innervation from the LC is prominent in the hippocampus (Moore and Bloom, 1979), where α1-adrenoceptors appear to mediate inhibitory effects of NE released by LC stimulation (Curet and de Montigny, 1988; Mody et al., 1983). It has been suggested that NE functions as an endogenous anticonvulsant (McNamara, 1980). Acting through α1-adrenoceptors, NE exerts an inhibitory effect in hippocampal kindling (Bengzon et al., 1990) and on seizure activity induced by N-methyl-D-aspartic acid (NMDA) (Wu et al., 1987). Kindling is suppressed by infusions of α1-adrenergic agonists into the amygdala/pyriform brain region; on the other hand, infusions of α-adrenergic antagonists promote kindling (Pelletier and Corcoran, 1993).

Seizures have been reported to be associated with inhibition of the normal functioning of the phosphoinositide second messenger-generating system (Jope, 1991). In the brain, both M1 muscarinic and α1-adrenergic receptor signals are transduced by second messengers that are generated by hydrolysis of phosphoinositides (PI) (Michell, 1975; Berridge, 1984; Schoepp et al., 1984). The two second messengers produced by hydrolysis of phosphatidylinositol bisphosphate are diacylglycerol (DAG) and inositol 1,4,5-trisphosphate (IP3). IP3 stimulates release of calcium from intracellular stores, and DAG activates protein kinase C (PKC). Activation of PKC in turn induces feedback inhibition of agonist-stimulated PI metabolism and thus can serve as a mechanism for modulating excitability (Drouva et al., 1991).