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BRIEF COMMUNICATION

Phorbol Esters and Forskolin Infused Into Midbrain Central Gray Facilitate Lordosis

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MOBBS, C. V., J. M. ROTHFELD, R. SALUJA AND D. W. PFAFF. *Phorbol esters and forskolin infused into the midbrain central gray facilitate lordosis.* PHARMACOL BIOCHEM BEHAV **34**(3) 665–667, 1989.—Several peptides, when infused into the MCG, facilitate lordosis in estrogen-primed female rats. Since these peptides can act through cAMP and/or protein kinase C, and these second messenger systems have been implicated in neuromodulation, this study examined if pharmacological agents which stimulate these systems would facilitate lordosis. Ovariectomized female Fisher rats were given bilateral cranial cannulae targeted to the MCG, or cortex dorsal to MCG, and allowed at least a week to recover. Forty-eight hours after injection of 1.25 μg estradiol benzoate (EB), 1 μl of each of the following was infused into the MCG (n=8–12): 1) forskolin (5 μg/μl 50% DMSO); 2) phorbol-20-oxo-20-deoxy-12,13-dibutyrate (PBu; 5 μg/μl 50% DMSO); 3) both forskolin and PBu (2.5 μg of each/μl); 4) vehicle (50% DMSO). In a separate study of identical design, 1 μl of another phorbol ester (12-myristate 13-acetate) was infused into the MCG of EB-primed rats. Forskolin and phorbol esters each facilitated lordosis maximally at 60–90 minutes after infusion. Combining both agents also facilitated lordosis, and vehicle had no effect. These results suggest that infusing agents which stimulate cAMP and protein kinase C into the MCG can facilitate lordosis in estrogen-primed female rats.

Lordosis Midbrain central gray Protein kinase C Phorbol ester cAMP Forskolin

INFUSION of LHRH and substance P into the midbrain central gray (MCG) will facilitate lordosis in estrogen-primed rats (2,13), and responses to these peptides in nonneuronal tissues may involve protein kinase C or cAMP (1, 5, 10, 15). These second messenger systems have been implicated in several models of neuromodulation (6). However, the types of second messenger systems associated with these peptides could differ with the receptor subtype and the tissue or brain area studied, so it is not known if these systems mediate effects of peptides on lordosis. No study has examined the effects on lordosis of infusing into the MCG agents which directly stimulate cAMP or protein kinase C. The biological effects of forskolin and phorbol esters are thought to be largely, if not entirely, due to their ability to increase adenylate cyclase and protein kinase C activity, respectively (11,14). We report here that, when infused into the MCG, both forskolin and phorbol esters will facilitate lordosis in estrogen-primed rats.

METHOD

Ovariectomized female Fisher rats (Charles River) weighing 160–180 g were housed in air-conditioned quarters on a 12/12 LD cycle (lights off at 1200 hr) and given Purina rat lab chow and water ad lib. One week after ovariectomy rats were implanted stereotaxically with bilateral cranial guide cannulae (22-gauge) fitted with a removable, solid internal guide (Plastic Products, Roanoke, VA) extending approximately 0.5 mm below the outer guide. Animals were anesthetized with Chloropent (Fort Dodge; 3 ml/kg) and placed in a stereotaxic frame. Upon exposure of the cranium and removal of bone the bilateral cannulae (2.5 mm between tips) were targetted to the MCG with the following coordinates: 1.3 mm rostral to lambda and 4.5 mm below dura, lowered at a 10 degree angle directed rostrally; cannulae were then cemented in skull. For control rats with cannulae targetted to cortex, the coordinates were the same except the cannula tips were placed 2.0 mm below dura. These coordinates were originally based on König and Klippel (7), but have been refined empirically to provide the most reliable placement into the dorsal MCG of female rats weighing approximately 175 g.

Behavioral Testing

One week after cannulation rats were injected SC with 1.25 μg estradiol benzoate (Sigma). The lordotic response was determined using the manual stimulation technique. Manual stimulation was performed as described previously (4,12). Briefly, rats were placed in a 10 × 30 cm cage and the lordosis reflex was determined