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EFFECT OF MATERNAL MORPHINE ADMINISTRATION ON NEONATAL RAT BRAIN ORNITHINE DECARBOXYLASE (ODC)

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INTRODUCTION

Ornithine decarboxylase (EC 4.1.1.17) catalyzes the conversion of ornithine to the diamine putrescine, the first and perhaps rate-limiting step in polyamine biosynthesis (1,2). In a variety of rapidly growing systems from bacteria (3-5), D. Melanogaster (6,7) and amphibian embryo (8), to chick embryo (9-11) regenerating mouse and rat liver (12-15) and central nervous system (16,17), polyamines and nucleic acids vary in a parallel fashion. Stimulation of animal and bacterial RNA polymerase in vitro by physiologic concentrations of polyamines has been well documented (18-20). Recent evidence suggests that polyamines are stimulated by cyclic-AMP (21,22) and may act as a primary "second messenger" replacing the cortisol requirement of mouse mammary gland in tissue culture (23).

Anderson and Schanberg have shown that fetal and neonatal rat brain has a characteristic ornithine decarboxylase (ODC) developmental pattern which is sensitive to hormonal manipulation, and have suggested that perturbations of this pattern may be an early and easily determined index of central nervous system maturation (24,25). Morphine has a variety of effects on protein and nucleic acid metabolism (26). The purpose of this study was to determine whether maternal morphine administration affects the brain developmental ODC pattern in the pups.

METHODS

Gravid Sprague-Dawley (Zivic-Miller) rats were obtained 10 days post-fertilization, caged separately, and given food and water ad lib. Thirteen days post-fertilization, subcutaneous injections of morphine hydrochloride were begun. Animals were given 2.5 mg/kg every 12 hr and the dose was doubled every 2 days until 40 mg/kg was being administered

per injection (first day post-partum) and then maintained at this level for the remainder of the study. Controls received equal-volume injections of normal saline.

ODC was determined as previously reported (24), with the slight modification of 0.5 mM pyridoxal phosphate and 0.5 mM dithiothreitol being added to the incubation mixture.

RESULTS AND DISCUSSION

As shown in Table 1, pups of morphine-treated mothers have a higher level of ODC at every time point examined. Further, the difference between pups of morphine-treated mothers and controls appears to increase with age. This delay in the postnatal fall of ODC is similar to that reported when cortisol was administered to neonatal rat pups, and is consistent with a delay in central nervous system maturation (25). It can also be seen from Table 1 that total wet weight of brain in experimental pups was below that of controls, with the per cent decrease (10%) remaining fairly consistent at the later time points.

Table 1. Effect of maternal morphine administration on the developing brains of offspring

Postnatal age (days)	N	ODC activity (% control ± S.E.M.)	Wet weight of brain (%) (control ± S.E.M.)
2	17	128 ± 7	99 ± 5
5	20	168 ± 12*	84 ± 5‡
10	19	194 ± 10‡	89 ± 4
18	18	309 ± 7‡	91 ± 2†

*$P < 0.05$ ‡$P < 0.025$ †$P < 0.001$

Clinical studies suggest that infants of opiate-addicted mothers have a variety of central nervous system difficulties and in several animal species opiates seem to be associated with growth retardation and developmental central nervous system abnormalities (27-33) Opiates alter CNS protein synthesis *in vivo* and *in vitro* (34-36). Whether the opiates are working directly through ODC to alter protein synthesis or the altered ODC is merely an early reflection of modified protein synthesis is unclear. Another possibility would be that these drugs affect ODC indirectly through hormonal mechanisms. This latter possibility is especially interesting since morphine administration is well recognized to cause an increase in serum glucocorticoids and, as was pointed out above, administration of cortisol in the neonatal period causes a delay in the maturation pattern of ODC similar to that reported above when morphine is administered (25,36).

Our findings of an altered ODC pattern in the brains of pups of drug-treated mothers

support the hypothesis that chronic opiate administration to the pregnant or lactating female interferes with the biochemical maturation of brain in the offspring. Further, our findings give additional support to the use of ODC as a sensitive index of CNS maturation.

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