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DIFFERENTIAL EFFECTS OF PRENATAL AND POSTNATAL ACTH OR NICOTINE EXPOSURE ON 5-HT HIGH AFFINITY UPTAKE IN THE NEONATAL RAT BRAIN

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Abstract—These studies were designed to examine the differential effects of prenatal or postnatal administration of ACTH 1-39 and nicotine, on 5-HT high affinity uptake in brainstem and hippocampal synaptosomes. ACTH was administered prenatally (to pregnant dams) and postnatally to the neonates. Postnatal administration of ACTH significantly increased high-affinity 5-HT uptake in the hippocampus and especially the brainstem at both 7 and 21 days after birth. Prenatal ACTH, on the other hand, transiently increased 5-HT uptake in only the brainstem at 7 days, a change that was reversed at 21 days. While the effects of postnatal nicotine administration were essentially the same as those of postnatal ACTH treatment, prenatal nicotine, unlike ACTH, did not alter 5-HT uptake in 7-day-old rats but did reduce uptake in both tissues at 21 days. The observation that postnatal nicotine mimics the effects of postnatal ACTH and that nicotine stimulates ACTH release, suggests that the postnatal effects of nicotine may be exerted through ACTH.

Key words: nicotine, ACTH, 5-HT, development, neonatal, brain.

Although the effects of nicotine on brain neurotransmitter systems have been extensively investigated, the influence of this potent alkaloid on the serotonergic system is unclear. There are reports that indicate that nicotine administration to adult rats causes significant increases in hypothalamic serotonin (5-HT)[9] whereas other studies indicate that there is a regionally selective reduction in hippocampal 5-HT content following exposure to nicotine treatment.[6–8] In a recent study, Fitzgerald *et al.*[16] have demonstrated that nicotine-induced hyperactivity was reduced by *para*-chlorophenylalamine (CPA; a 5-HT synthesis inhibitor), suggesting that serotonin is involved in the effects of low doses of nicotine on locomotor activity in rats. Thus, while the precise interaction between nicotine and serotonin is still unknown, these studies point to a possible interaction of these two systems in adult animals.

Much less is known about the effects of nicotine on the developing serotonergic system. Nicotine administration causes the release of ACTH in adult animals and humans,[11,12,21,35] and more recently in neonates.[22] Several studies have shown that during early postnatal development rat pups respond to ACTH and stressors by increasing corticosterone levels.[13,27] On the other hand, there is evidence that similar stressors do not elicit a comparable response by the middle of the first week of postnatal life.[10,13,19] This period of adrenocortical quiescence during early development has been referred to as the 'stress-non-responsive period' or SNRP.[32] The phenomenon of SNRP has generated much thdoretical as well as practical interest. To date, the model of Sapolsky and Meaney[31] has been most successful in explaining this phenomenon. In their model the profile of the hierarchical scheme that accounts for SNRP includes the hippocampus. Therefore, it is of interest to determine whether early stress may alter the development of the hippocampus through changes in the serotonergic system which is a main input in this region. Since the hippocampus undergoes a significant amount of postnatal development[24] and possesses a large number of nicotine receptors[33,36] as well as serotonin terminals,[4] this study was designed, in part, to evaluate the effects of early nicotine treatment on the neuronal maturation of the hippocampal serotonergic system.

The second objective of this study was to investigate whether early stress, as mimicked by treatment with the stress-evoked hormone, adrenocorticotropic hormone (ACTH), altered the maturation of the serotonergic system in a manner similar to that observed with early exposure to nicotine, since nicotine is itself a potent stressor.[22,23] In this study, nicotine was administered in a

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