Prenatal Cocaine Potentiates the Effects of Morphine in Adult Mice

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Summary—Prenatal cocaine exposure has been reported to result in abnormal neurobehavioral development, both in animals and humans. In this study, outbred CD-1 mice were exposed in utero to cocaine hydrochloride administered daily as i.p. injections to dams from day 10 of gestation to day 16, at the dose 0, 5 or 50 mg/kg. Cocaine did not alter duration of pregnancy while it decreased the difference in maternal body weight from days 10 to 16 in the dams receiving the higher dose of cocaine. The body weight of the offspring from birth to 15 days of age and the physical maturation were not affected by prenatal cocaine exposure. The development of the response to strong tactile stimulation was either slightly delayed in the 5 mg/kg group or markedly accelerated in the 50 mg/kg group. At adulthood, animals were assessed for behavioral responses to a novel environment, for response to painful stimulation (hot-plate test set at 55 ± 1°C), and for the effects of a single morphine injection (30 mg/kg, i.p.). Data showed that in the absence of prenatal cocaine exposure effects, morphine increased the time spent in inactivity, while it decreased rearing, grooming and bar-holding behaviors. In the case of sniffing, morphine increased this behavior, except in the 5 mg/kg cocaine group. Moreover, morphine administration induced the expected increase of locomotion, irrespective of prenatal condition. With respect to pain reactivity, prenatal cocaine exposure resulted in an increase of licking latency in the 5 mg/kg group. Morphine administration before the hot-plate test, induced the expected analgesia, which was particularly evident in mice receiving 5 mg/kg of cocaine. The present results suggest that gestational cocaine exposure is associated with changes in development of sensory response and with an enhancement of the sensitivity to morphine.

Keywords—Behavioral development, pain reactivity, locomotor/exploratory activity, prenatal cocaine, morphine.

In the last years, cocaine has received particular attention (Gawin, 1991; Johanson and Fischman, 1989) because of its increasing abuse, particularly in Western countries (Kleber, 1988). The use of cocaine during pregnancy has stimulated a number of clinical and animal studies to characterize the neurobehavioral and developmental deficits in human infants (Chasnoff et al., 1985; 1989) and rats (Dow-Edwards et al., 1990; Sobrian et al., 1990). The teratogenicity of prenatal cocaine administration is still controversial. While some studies have observed no signs of toxicity following prenatal cocaine exposure (Fantel and MacPhail, 1982), others have reported structural defects, morphological abnormalities, neurobehavioral deficits and other functional effects, both in rats and mice (Church et al., 1988; Church and Overbeck, 1991; Heyser et al., 1990; Mahalik et al., 1980; 1984; Spear et al., 1989). Lasting alterations in the functional activity of several rat brain regions and neurochemical changes such as a long-lasting increase in opiate receptor binding as well as alterations of the dopaminergic system have been reported to follow prenatal cocaine exposure (Clow et al., 1991; Dow-Edwards et al., 1990). A functional linkage between the dopaminergic and opioid systems has been suggested, whereby cocaine-induced alterations of the dopaminergic system can regulate the developing opioid system in the brain, thus manipulation of one system affects the other. For example, chronic cocaine treatment alters opiate receptor density in critical dopaminergic reward regions in the adult rat (Hammer, 1989). In addition, prenatal dopamine receptor blockade produced by haloperidol exposure decreases striatal opiate receptor binding (Moon, 1984). Prenatal cocaine administration results in an up-regulation of opiate receptor binding in the rat brain, since rat pups exposed perinatally to cocaine and challenged postnatally with morphine emitted fewer ultrasounds than the corresponding