# Assessment of the Effects of Developmental Toxicants: Pharmacological and Stress Vulnerability of Offspring

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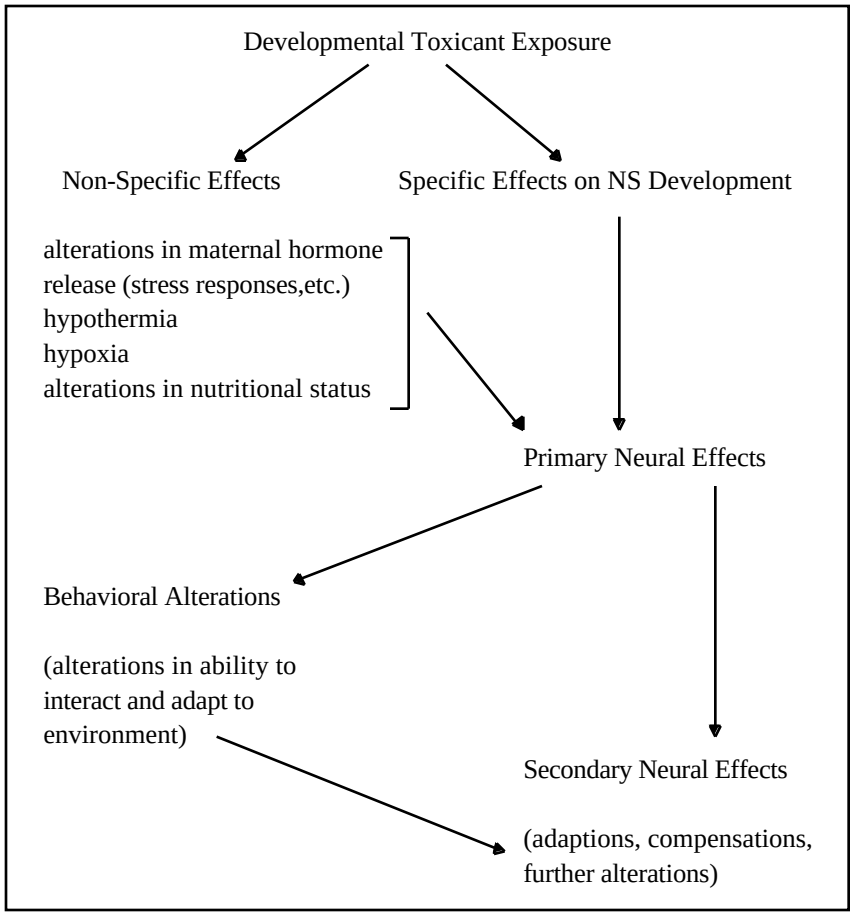
In developmental toxicology studies, behavioral testing of offspring typically is conducted in carefully controlled situations characterized by minimal environmental stressors and distractors. However, increasing the demands of the test situation through the use of environmental or pharma-cological challenges may reveal or unmask deficits that may not be evident under basal testing conditions. The purpose of this chapter is to discuss how assessment of pharmacological and stress vulnerability has proved to be useful in revealing alterations in offspring exposed to developmental toxicants. Studies of prenatal exposure to ethanol and cocaine in the laboratory rat are used as examples.

## NERVOUS SYSTEM ADAPTATION AFTER DEVELOPMENTAL INSULTS

Table 1 presents a simplistic outline of how developmental toxicants may influence neural development. Exposure to a developmental toxicant may have a number of specific effects and various nonspecific effects that ulti-mately can affect nervous system development. Together these specific and nonspecific effects lead to a pattern of primary neural alterations that may emerge during or shortly after exposure to the neurotoxicant. These primary neural effects may lead to alterations in the ability of the organism to interact and adapt to the environment, which may lead to further neural alterations. But, particularly important for the purposes of this chapter, the primary neural alterations themselves may result in secondary neural adaptations as the nervous system attempts to adjust and compensate for these initial neural alterations.

The nervous system is a highly interactive and intrinsically self-regulating system that is often homeostatically driven. Manipulating nervous system activity at any stage of life may lead to compensatory adaptations




in other components of the nervous system, although the nature of those compensatory processes appears to vary not only with the nature of the insult but also with age at the time of the insult. As an example of the latter, chronic blockade of dopamine (DA) receptors in adulthood leads to an upregulation in DA receptor binding (Burt et al. 1977), whereas chronic blockade of these receptors early in development results in a decrease in DA receptor binding (Rosengarten and Friedhoff 1979). Simplistically, it is as if chronic receptor blockade induces receptor upregulation in adulthood in an apparent attempt to maintain homeostatic equilibrium in the DA system; conversely, during development fewer receptors may be formed because fewer appear to be needed due to the chronic presence of the DA antagonist. (See Spear and Scalzo 1986 for further review and discussion.)

The remarkable capacity of the nervous system to adapt to insults has been recognized for decades as an important principle in the field of developmental toxicology. For instance, as stated by Hughes and Sparber (1978, p. 366) 25 years ago: "Mammalian organisms frequently retain apparently normal function after extensive lesions of the CNS with functional reorganization and subsequent recovery of function occurring after destruction of as much as 98 percent of some brain regions." Yet, there may be a cost to such reorganization, with this cost being reflected by a decrease in adaptability. Certain behavioral and physiological functions may appear normal under basal testing conditions, but underlying deficits may be unmasked when subjected to challenges of various kinds. (See Hughes and Sparber 1978 for further discussion.)

## TYPES OF CHALLENGES THAT MAY REVEAL UNDERLYING DEFICITS

If the nervous system is often capable of showing at least partial functional reorganization and recovery after exposure to a developmental insult, then exposing the drug-exposed offspring to challenges may unmask deficits that may not be evident under baseline testing conditions. A variety of types of challenges potentially can be used to reveal or unmask underlying deficits. Among the types of challenges that may be useful include assessment of responsiveness to pharmacological chal-lenges, adaptability and responsivity to stressors, age-related alterations, and the ability to recover from subsequent brain damage. The first two of these challenges have been most frequently examined and are the focus of this chapter, although the other approaches listed are also promising. For instance, neural alterations that normally occur with aging may be accelerated or exacerbated after exposure to developmental toxicants. Moreover, exposure to a developmental toxicant may constrain subsequent adaptability in response to later brain damage. For instance, Gottesfeld and colleagues (1989) observed that prenatal ethanol exposure led to a suppression of the normal plasticity seen in dopaminergic terminals in the olfactory tubercle following olfactory bulbectomy. This approach of examining how early neurotoxicant exposure alters later nervous system recovery from brain damage is an interesting one that has been little investigated to date.

In focusing on the first two types of challenges, findings derived from research examining the effects of prenatal exposure to ethanol and

cocaine exemplify these approaches. Ethanol was chosen because there is a fairly large database of animal studies collected over the past 2 decades examining this substance. Cocaine was chosen as the second example because this substance is a particular focus of much current research, although it should be recognized that there is a more limited database with this compound, with most of the animal work in this area published only in the past 5 years. Findings are illustrated using a few examples of work from the author's laboratory examining the developmental toxicology of cocaine in rats.

## Pharmacological Challenges

There are two basic approaches that have been used with regard to pharmacological challenges. The first approach has been to use neuro- and psychopharmacological challenges to assess functional alterations in specific neurotransmitter systems induced by the developmental toxicant. This approach has been used extensively in alcohol research and has been useful, in conjunction with neurochemical studies, in documenting alterations in a variety of neurotransmitter systems including the dopaminergic, cholinergic, and serotonergic systems following prenatal ethanol exposure (Bond 1985, 1986a, 1986b). This approach is beginning to be used in cocaine research as well. For instance, researchers have found that prenatal cocaine exposure results not only in increases in opiate binding in many brain regions (Clow et al. 1991), but also an increased responsiveness to a variety of opiate receptor agonists, particularly mu opiate agonists (Goodwin et al. 1993). Gestational cocaine exposure also increases dopamine type 2 (D2) receptor binding (Scalzo et al. 1990) and results in an increased psychopharmacological sensitivity to the D2 receptor agonist quinpirole (Moody et al. 1992).

The second pharmacological approach is to assess postnatal responsiveness to the same drug that was administered prenatally. Basically, the question is whether offspring exhibit a decreased sensitivity (i.e., tolerance) or an increased sensitivity (i.e., sensitization) to the drug to which they were exposed early in life. This approach is of special interest with regard to subsequent drug self-administration: Does early exposure to a drug increase or decrease later self-administration of that substance?

## Sensitivity to Later Ethanol Challenge After Prenatal Ethanol Exposure

Table 2 presents a summary of representative findings regarding how prenatal ethanol exposure influences later sensitivity to ethanol challenges. As shown, the effects of early ethanol exposure on later

TABLE 2. Sensitivity to later EtOH challenge after prenatal EtOH exposure.

| Response | Sensitivity | Reference |
|---|---|---|
| Hypothermia | Decreased | Anandam et al. 1980<br>Abel et al. 1981<br>Molina et al. 1987 |
| | Increased | Taylor et al. 1983 |
| Hypnotic | No change | Abel 1979<br>Randall and Bogan 1980<br>Perez et al. 1983<br>Randall et al. 1983 |
| Later EtOH intake | Increased | Bond and DiGiusto 1976<br>Phillips and Stainbrook 1976<br>Randall et al. 1983<br>Molina et al. 1987 |
| | No change | Abel and York 1979 |

ethanol sensitivity appear to depend upon the response measure used. For instance, although there appears to be general consensus that prenatal ethanol exposure does not alter the later hypnotic effects of ethanol as indexed by ethanol-induced sleep times (Abel 1979; Perez et al. 1983; Randall and Boggan 1980; Randall et al. 1983), such exposure has been observed to alter ethanol-induced hypothermia. There is not perfect concordance across laboratories, however, in terms of the nature of the alterations in ethanol-induced hypothermia that are seen in offspring exposed gestationally to ethanol. Whereas most studies have found that prenatal ethanol exposure decreases sensitivity to the later hypothermic effects of ethanol (Abel et al. 1981; Anandam et al. 1980; Molina et al. 1987), Taylor and colleagues (1983) reported an increased hypothermic effect to a later challenge dose of ethanol in these offspring. Differences among laboratories that might have led to these discrepant results are not readily apparent.

As can be seen in table 2, the majority of studies of later ethanol intake have reported that prenatal alcohol exposure increases alcohol self-administration in adulthood (Bond and DiGiusto 1976; Molina et al. 1987; Phillips and Stainbrook 1976; Randall et al. 1983), although this finding is not ubiquitous (Abel and York 1979). It should be recognized that most of these studies examining ethanol intake have used two bottle intake tests where the amount of ethanol consumed is generally without pronounced pharmacological consequences, and

where such intake could be influenced by flavor factors and taste neophobia rather than the pharma-cological consequences of ethanol per se. Thus, although the data to date are consistent with the suggestion that early ethanol exposure may gener-ally increase later ethanol self-administration, these findings need to be confirmed using other procedures for the initiation of ethanol intake and for the control of taste sensitivity/neophobia.

## Sensitivity to Later Stimulant Challenge After Prenatal Cocaine Exposure

With regard to sensitivity to stimulants (cocaine and amphetamine) after prenatal cocaine exposure, less consensus has been reached, probably due in part to the more limited database available. As shown in table 3, in terms of stimulant-induced activity, decreases in sensitivity to stimulants have been reported in testing early in life (Meyer et al. 1992; Sobrian et al. 1990), whereas increases (Foss and Riley 1991; Peris et al. 1992) or no effect (Giordano et al. 1990; Heyser et al., unpublished) on stimulant-induced activity have been observed in adulthood. In terms of stimulant-induced startle effects, both decreased responsiveness in females (Hughes and Dow-Edwards 1992) and no effect (Foss and Riley 1991) have been reported. In general, in those instances where altered sensitivity to stimulants has been observed on activity or startle tests in adulthood, it appears that these effects are relatively modest. With regard to other response measures, the author and coworkers have observed that cocaine-exposed offspring are somewhat less sensitive to the discriminative stimulus effects of cocaine (Heyser et al., unpublished) and are less sensitive to the reinforcing properties of cocaine as indexed by cocaine-induced conditioned odor preferences in infancy (Heyser et al. 1992a) and cocaine-induced conditioned place preferences (CPP) in adulthood (Heyser et al. 1992b). Such deficits in cocaine-conditioned preferences presumably reflect an apparent reduction in the reinforcing efficacy of cocaine that may be related to a possible alteration in drug abuse liability.

The basic principle behind the CPP procedure is that when drug administration is paired with a particular place on a number of occasions, animals develop a preference for that location to the extent that they find the drug reinforcing. In the study by Heyser and colleagues (1992b),

TABLE 3. Sensitivity to later stimulant challenge after prenatal cocaine exposure.

| Response | Sensitivity | Reference |
|---|---|---|
| Stimulant-induced activity | | |
| In infancy | Decreased | Sobrian et al. 1990<br>Meyer et al. 1992 |
| In adulthood | Increased | Foss and Riley 1991<br>Peris et al. 1992 |
| | No effect | Giordano et al. 1990<br>Heyser et al. 1994 |
| Stimulant effects on startle | Decreased (females) | Hughes and Dow-Edwards 1992 |
| | No effect | Foss and Riley 1991 |
| Cocaine discriminability | Decreased | Heyser et al. 1994 |
| Cocaine-induced preferences | | |
| In infancy (odor pref.) | Decreased | Heyser et al. 1992a |
| In adulthood (CPP) | Decreased | Heyser et al. 1992b |

offspring from three groups of dams were studied: dams subcutaneously injected with 40 milligrams per kilogram per 3 milliliters (mg/kg/ 3mL) daily on gestational days 8 through 20 (C40); dams injected daily with saline and whose daily food and water intake was paired with that of cocaine-exposed dams (PF—this pair-fed nutritional control group was used to control for the transient anorexia seen in cocaine-exposed dams at the onset of treatment); and untreated control dams given ad libitum access to lab chow (LC). Adult offspring from each prenatal treatment group were exposed 30 minutes a day to a white chamber and to a black chamber. For half of the animals, the black chamber was always paired with a saline injection, whereas the white chamber was paired with an injection of either saline or 2 or 5 mg/kg cocaine. The other half of the animals received these injections in the opposite chambers. On the test day, animals were not injected prior to being given a 15-minute prefer-

ence test where the amount of time spent in each of these chambers or a novel gray chamber was recorded.

Normal adult animals exhibit a CPP for cocaine—that is, on the test day animals that received cocaine in a particular chamber spend more time in that chamber than animals that received saline injections in that chamber. Indeed, as shown in figure 1, LC control animals that received 2 or 5mg/kg cocaine during conditioning exhibited significant place prefer-ences in both the black and white chambers. Similarly, PF control animals that received 5 mg/kg in the black chamber and 2 mg/kg in the white chamber during training also exhibited significant place preferences. In contrast, no evidence of a cocaine-induced place preference was seen in adult offspring prenatally exposed to cocaine when trained with either dose of cocaine in either chamber. A similar deficit was seen in cocaine-exposed offspring when tested in infancy for the development of cocaine-induced conditioned odor preferences (Heyser et al. 1992a).

There are several possible explanations of these findings. The lack of significant CPP in the cocaine-exposed offspring could reflect a learning deficit. This possibility, however, is rather unlikely; it was previously shown that adult cocaine-exposed offspring do not differ from controls in their ability to learn a rather complex conditional discrimination task (Heyser et al. 1992c). It also does not appear that this deficit in the formation of cocaine-induced CPP is related to any alteration in cocaine pharmacokinetics in these animals; no differences were found among C40, PF, and LC offspring in brain levels of cocaine at any time examined (5 to 60 minutes postinjection) following intraperitoneal administration of a challenge dose of 10 mg/kg cocaine in adulthood (Heyser et al. 1994). A final possibility is that this lack of cocaine-induced CPP may reflect an attenuation in the reinforcing consequences of cocaine in these animals.

These data may reflect an alteration in drug abuse liability in the cocaine-exposed offspring. Although there are some exceptions, manipulations that decrease CPP generally increase self-administration and vice versa. (See Le Moal and Simon 1991 for references and discussion.) The typical interpretation of these findings is that manipulations which decrease the

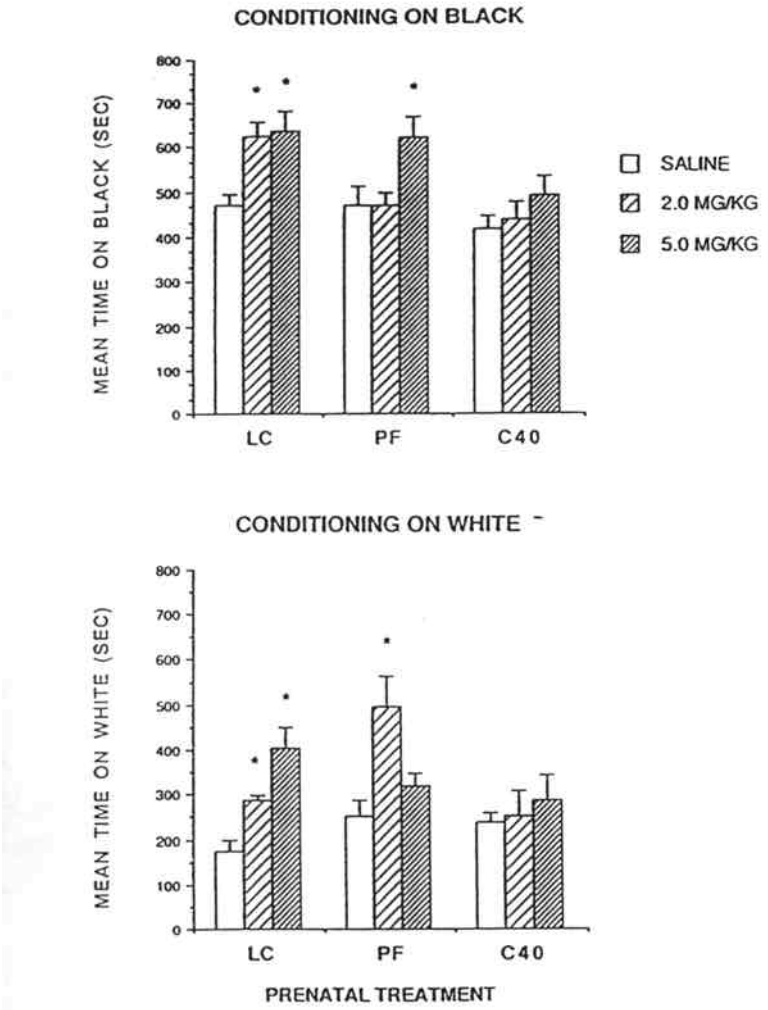



**FIGURE 1.** Mean time (seconds) spent on the test day in the previously drug-paired compartment when animals from each prenatal treatment group (C40 = cocaine; PF = pair-fed; LC = nontreated control) were conditioned in black (top) and white (bottom). Place conditioning was defined to occur if the animals conditioned with cocaine spent significantly more time in the drug-paired chamber than animals receiving saline ($^{*}$=$p<0.05$ for these comparisons).

**SOURCE:** Reprinted from *Neurotoxicology and Teratology*, Vol.14, Heyser, C.J.; Miller, J.S.; Spear, N.E.; and Spear, L.P. "Prenatal cocaine exposure disrupts cocaine-induced conditioned place preference in rats." pp. 57-64, Copyright, 1992, with kind permission from Pergamon Press Ltd, Headington Hill Hall, Oxford OX3 OBW, UK.

reinforcing properties of a drug result in increased drug self-administra-tion because higher doses of the drug are necessary to compensate for the decreased rewarding efficacy of the drug. That is, because the animals find the drug less reinforcing, they self-administer more of the drug to obtain its psychoactive consequences (Le Moal and Simon 1991). Taken together, these findings raise the possibility that the decrease in cocaine-induced odor and place preferences seen in offspring exposed gestation-ally to cocaine (Heyser et al. 1992a, 1992b) may be associated with an increase in the later self-administration of cocaine. This possibility should be considered speculative until directly tested using intravenous (IV) self-administration protocols.

Stress Responsivity

A second challenge that may help unmask underlying neural alterations induced by developmental toxicants is assessment of stress responsivity. This type of challenge has been shown to be a sensitive and robust indicator of the effects of prenatal ethanol and cocaine exposure.

Responsivity to Stressors after Prenatal Ethanol Exposure. Prenatal exposure to ethanol has been shown to alter later stress responsivity. As shown in table 4, these findings are remarkably consistent across studies. In infancy, offspring prenatally exposed to ethanol exhibit increased plasma and brain corticosterone levels and a blunted pituitary-adrenocortical response to stressors such as injection, ether, and ethanol challenge that lasts for at least the first postnatal week (Taylor et al. 1982, 1986; Weinberg 1989). By contrast, when tested in adulthood, these ethanol-exposed offspring showed no alterations in basal corticosterone levels but exhibited a hyperresponsive pituitary-adrenal response to stressors such as footshock, ether, and ethanol challenge (Nelson et al. 1986; Taylor et al. 1982; Weinberg 1988; Weinberg and Gallo 1982; Weinberg et al. 1986). These hormonal effects are robust, particularly in female offspring, and have been replicated across labora-tories. Offspring exposed prenatally to ethanol have not been assessed for their behavioral responsiveness to stressors as frequently as they have been assessed hormonally. Nevertheless, the available evidence suggests that gestational ethanol exposure also alters behavioral adaptability to stressors in adulthood as indexed by decreased immobility in swim tests (Bilitzke and Church 1992; Nelson et al. 1984).

TABLE 4. Responsivity to stressors after prenatal EtOH exposure.

| Response measure | Reference |
|---|---|
| Hormonal alterations to stress | |
| In infancy | |
| Increased corticosterone levels - birth | Taylor et al. 1982, 1986<br>Weinberg 1989 |
| Blunted pituitary-adrenal response to stressors | Taylor et al. 1986<br>Weinberg 1989 |
| In adulthood | |
| No alteration in basal corticosterone | Taylor et al. 1982<br>Weinberg et al. 1986<br>Weinberg 1988 |
| Hyperresponsive pitituary-adrenal response to stressors | Taylor et al. 1982<br>Weinberg and Gallo 1982<br>Nelson et al. 1986 |
| Altered behavioral adaptability to stress | |
| In adulthood | |
| Decreased immobility in swim tests | Nelson et al. 1984<br>Bilitzke and Church 1992 |

Responsivity to Stressors after Prenatal Cocaine Exposure. Altered responsivity to stress also appears to be a robust and reliable finding in studies of prenatal cocaine exposure (table 5), although the focus to date has been on behavioral rather than hormonal assessments. These findings are particularly notable in that they may represent the clearest example of replicable findings at this early stage of animal research in the developmental toxicology of cocaine. Like ethanol-exposed offspring, adult offspring prenatally exposed to cocaine do not differ in basal corticosterone or adrenocorticotropic hormone (ACTH) levels (Cabrera et al. 1993; Kuhn and Spear, unpublished observations); to the author's knowledge, there are no publications to date regarding pituitary-adrenal stress responsivity in these animals. However, in terms of behavioral responsivity to stress, there are a number of reported alterations in cocaine-exposed offspring in their acute and long-term

TABLE 5. Responsivity to stressors after prenatal cocaine exposure.

| Response measure | Reference |
|---|---|
| Hormonal | |
| No alterations - basal ACTH or corticosterone level | Cabrera et al. 1993<br>Kuhn and Spear (unpubl. observ.) |
| Behavioral | |
| Decreased immobility | |
| Swim tests | Bilitzke and Church 1992 |
| During intermittent shock exposure | Molina et al. 1994 |
| | Molina et al. 1994 |
| Altered behavioral responsivity following prior footshock | |
| Decreased open field immobility | Molina et al. 1994 |
| Increased reactivity to later footshock | Smith et al. 1989 |
| "Frantic swimming" - water maze tasks | McMillen et al. 1991<br>Johns et al. 1992<br>Smith (personal commun., 1992) |

responses to a variety of stressors. Among the notable behavioral alter-ations are decreases in immobility (Bilitzke and Church 1992; Molina et al. 1994) in response to acute stressors, as well as several longer lasting behavioral alterations following prior exposure to footshock (Molina et al. 1994; Smith et al. 1989). Increases in "frantic" behavior (Johns et al. 1992; McMillen et al. 1991; Smith, personal communication, 1992) also have been reported.

The results of a recent study illustrate these findings (Molina et al. 1994). In this study, adult male C40, PF, and LC offspring were assigned to one of three groups. Each animal in one group (FS) was given a 5-minute forced swim in room-temperature water on the first day; animals in the second group (SHOCK) were individually given

20 brief footshocks over a 10-minute period on this day; animals in the third group (CTRL) were not manipulated on the first day. All animals were then given a 5-minute open-field test on the second day. Normal adult animals, when exposed to a stressful situation such as a forced swim or intermittent footshock, exhibit an increase in immobility not only during the stressor, but also frequently after the stressor when confronted with a novel situation such as an open field (Armario et al. 1991; De Pablo et al. 1989; Van Dijken et al. 1992). According to Bolles (1970) and others (De Pablo et al. 1989; Fanselow 1986), this immobility is thought to be an adaptive response to stress.

As shown in figure 2a, cocaine-exposed offspring exhibited less immobility than control offspring during the forced swim test, thereby replicating findings reported previously by Bilitzke and Church (1992). Similarly, cocaine-exposed offspring also exhibited less immobility during the intermittent footshock exposure (see figure 2b). Moreover, when animals were tested 24 hours later in the open field, LC and PF control offspring that received prior exposure to footshock exhibited more immobility than their previously unstressed littermates (figure 2c). This increase in immobility induced by prior footshock was not seen in the cocaine-exposed offspring. Thus, both during and following exposure to an acute stressor, offspring subjected to cocaine prenatally exhibited less immobility than both groups of control offspring. To the extent that immobility is an adaptive species-specific defense response to stressors (see Bolles 1970), these data suggest that prenatal cocaine exposure may disrupt later stress adaptability. As noted in table 5, a number of studies report similar findings. This alteration in stress responsivity appears to be a robust and reliable finding, even given the limited number of investigations to date examining the behavioral toxicology of cocaine in animal models.

## SUMMARY AND CONCLUSIONS

From this brief summary of alterations in pharmacological and stress responsivity following gestational ethanol and cocaine exposure, a number of conclusions can be reached, although some of these conclusions are more speculative than others.

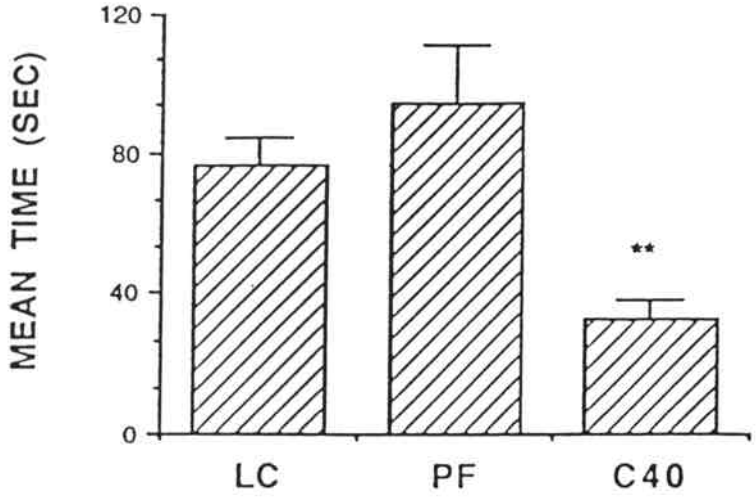



**FIGURE 2a.** Mean time (seconds) spent in immobility during A) the forced swim test, B) the footshock session, and C) the subsequent open field test by adult male offspring prenatally exposed to cocaine (C40), pair-fed control offspring (PF) and nontreated control offspring (LC) (n=8-11 per test condition and treatment group). In C) animals were previously submitted to one of three conditions 24 hours prior to the open field test: 5 minutes of forced swim (FS), 10 minutes of intermittent footshock (SHOCK); or non-manipulated (CTRL). Error bars indicate SEM's.

**KEY:** A): $^{**}p<0.001$ when compared with LC and PF groups;
B): $^{*}p<0.05$ when compared with LC and PF groups;
C): $^{*}p<0.05$ when compared with corresponding CTRL groups).

**SOURCE:** Data derived from Molina et al. 1994.

Both pharmacological challenges and stress responsivity have been shown to be sensitive to the effects of prenatal ethanol as well as prenatal cocaine exposure.

In terms of pharmacological sensitivity, there is some inconsistency in the findings obtained. Nevertheless, there is limited evidence to suggest that prenatal exposure to ethanol (and potentially cocaine) may increase later

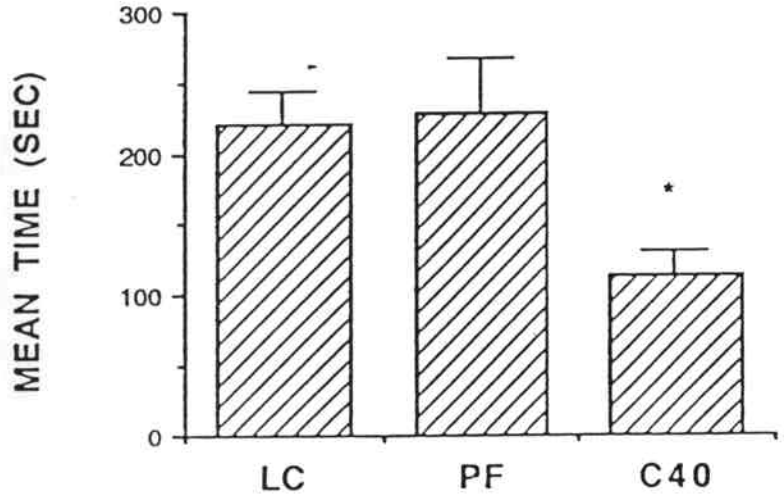



**FIGURE 2b.**

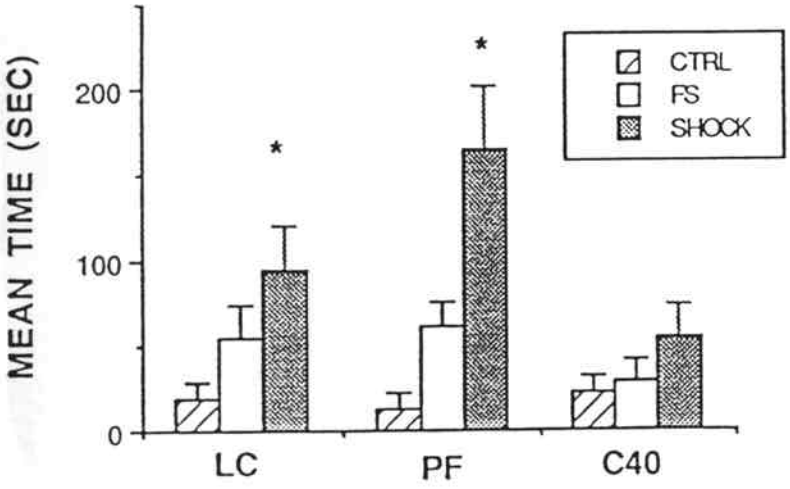



**FIGURE 2c.**

self-administration of the exposed drug. It should be recognized, however, that this possibility remains to be directly tested with cocaine, and needs further verification with ethanol using additional test procedures. It is interesting that a similar finding has been reported in the opiate literature: adult offspring exposed in utero to methadone exhibit an increase in subsequent morphine self-administration (Peters and Hovious 1983). Taken together, these data support the intriguing

but still specu-lative suggestion that early chronic exposure to a drug of abuse may increase the propensity for later self-administration of that or related substances. More systematic research is needed to test this possibility and to determine whether alterations may be seen in later self-administration of other classes of abused drugs—that is, whether early drug exposure may increase the later propensity for general drug abuse.

In terms of stress vulnerability, offspring exposed prenatally to ethanol predominantly have been assessed in terms of hormonal response measures, whereas the focus to date for offspring exposed prenatally to cocaine has been on alterations in behavioral responsivity to stressors. Yet prenatal exposure to either substance has been shown to result in consistent and long-lasting alterations in later responsivity to stressors in the absence of alterations in basal hormone levels in adulthood. For ethanol, these effects are particularly robust in female offspring; sex differences in stress responsivity in cocaine-exposed offspring have not been reported although few studies to date have been designed specifically to assess potential sex differences.

As previously noted, the nervous system has a remarkable capacity to reorganize following insults at any age. The cost of neural reorganization following developmental insults may be associated with a decrease in adaptability that may not necessarily be evident under basal, nondrug, minimal stress, low distractibility testing conditions. Yet it is perhaps worth noting that these are the very conditions under which subjects are tested. In future work in developmental toxicity, it may prove useful to increase the demands of testing by assessing offspring under challenge conditions to reveal or unmask deficits that are not evident under basal test situations.

## REFERENCES

Abel, E.L. Prenatal effects of alcohol on open-field behavior, step-down latencies and "sleep time." Behav Neural Biol 25:406-410, 1979.

Abel, E.L., and York, J.L. Absence of effect of prenatal ethanol on adult emotionality and ethanol consumption in rats. J Stud Alcohol 40(7):547-553, 1979.

Abel, E.L.; Bush, R; and Dintcheff, B.A. Exposure of rats to alcohol in utero alters drug sensitivity in adulthood. Science 212:1531-1533, 1981.

Anandam, N.; Felegi, W.; and Stern, J.M. In utero alcohol heightens juvenile reactivity. Pharmacol Biochem Behav 13:531-535, 1980.

Armario, A.; Gil, M.; Marti, J.; Pol, O.; and Balasch, J. Influence of various acute stressors on the activity of adult male rats in a holeboard and in the forced swim test. Pharmacol Biochem Behav 39:373-377, 1991.

Bilitzke, P.J., and Church, M.W. Prenatal cocaine and alcohol exposures affect rat behavior in a stress test (the porsolt swim test). Neurotoxicol Teratol 14:359-364, 1992.

Bolles, R.C. Species-specific defense reactions and avoidance learning. Psychol Rev 77:32-48, 1970.

Bond, N.W. Prenatal ethanol exposure and hyperactivity in rats: Effects of d-amphetamine and alpha-methyl-p-tyrosine. Neurobehav Toxicol Teratol 7:461-467, 1985.

Bond, N.W. Prenatal alcohol exposure and offspring hyperactivity: Effects of scopolamine and methylscopolamine. Neurobehav Toxicol Teratol 8:287-292, 1986a.

Bond, N.W. Prenatal alcohol exposure and offspring hyperactivity: Effects of para-chlorophenylalanine and methysergide. Neurobehav Toxicol Teratol 8:667-673, 1986b.

Bond, N.W., and DiGiusto, E.L. Effects of prenatal alcohol consumption on open-field behaviour and alcohol preference in rats. Psychopharmacology 46:163-165, 1976.

Burt, D.R.; Creese, I.; and Snyder, S.H. Antischizophrenic drugs: Chronic treatment elevates dopamine receptor binding in brain. Science 196:326-327, 1977.

Cabrera, T.M.; Yracheta, J.M.; Li, Q.; Levy, A.D.; Van de Kar, L.D.; and Battaglia, G. Prenatal cocaine produces deficits in serotonin mediated neuroendocrine responses in adult rat progeny: Evidence for long-term functional alterations in brain serotonin pathways. Synapse 15:158-168, 1993.

Clow, D.W.; Hammer, R.P.Jr.; Kirstein, C.L.; and Spear, L.P. Gestational cocaine exposure increases opiate receptor binding in weanling offspring. Dev Brain Res 59:179-185, 1991.

De Pablo, J.M.; Parra, A.; Segovia, S.; and Guillamon, A. Learned immobility explains the behavior of rats in the forced swimming test. Physiol Behav 46:229-237, 1989.

Fanselow, M.S. Conditioned fear-induced opiate analgesia: A competing motivational state theory of stress analgesia. Ann N Y Acad Sci 467:40-54, 1986.

Foss, J.A., and Riley, E. P. Failure of acute cocaine administration to differentially affect acoustic startle and activity in rats prenatally exposed to cocaine. Neurotoxicol Teratol 13:547-551, 1991.

Giordano, M.; Moody, C.A.; Zubrycki, E.M.; Dreshfield, L.; Norman,A.B.; and Sanberg, P.R. Prenatal exposure to cocaine in rats: Lack of long-term effects on locomotion and stereotypy. Bull Psychonom Soc 28:51-54, 1990.

Goodwin, G.A.; Moody, C.A.; and Spear, L.P. Prenatal cocaine exposure increases the behavioral sensitivity of neonatal rat pups to ligands active at opiate receptors. Neurotoxicol Teratol 15:425-431, 1993.

Gottesfeld, Z.; Garcia, C.J.; Lingham, R.B.; and Chronister, R.B. Prenatal ethanol exposure impairs lesion-induced plasticity in a dopaminergic synapse after maturity. Neuroscience 29(3):715-723, 1989.

Heyser, C.J.; Goodwin, G.A.; Moody, C.A.; and Spear, L.P. Prenatal cocaine exposure attenuates cocaine-induced odor preference in infant rats. Pharmacol Biochem Behav 42:169-173, 1992a.

Heyser, C.J.; Miller, J.S.; Spear, N.E.; and Spear, L.P. Prenatal exposure to cocaine disrupts cocaine-induced conditioned place preference in rats. Neurotoxicol Teratol 14:57-64, 1992b.

Heyser, C.J.; Spear, N.E.; and Spear, L.P. Effects of prenatal exposure to cocaine on conditional discrimination learning in adult rats. Behav Neurosci 106(5):837-845, 1992c.

Heyser, C.J.; Rajachandran, L.; Spear, N.E.; and Spear, L.P. Responsive-ness to cocaine challenge in adult rats following prenatal exposure to cocaine. Psychopharmacology 116:45-55, 1994.

Hughes, H.E., and Dow-Edwards, D.L. Prenatal cocaine exposure affects the acoustic startle response in adult rats. Teratology 45:527, 1992.

Hughes, J.A., and Sparber, S.B. d-Amphetamine unmasks postnatal consequences of exposure to methylmercury in utero: Methods for studying behavioral teratogenesis. Pharmacol Biochem Behav 8:365-375, 1978.

Johns, J.M.; Means, M.J.; Anderson, D.R.; Means, L.W.; and McMillen,B.A. Prenatal exposure to cocaine II: Effects on open-field-activity and cognitive behavior in Sprague-Dawley rats. Neurotoxicol Teratol 14:343-349, 1992.

Le Moal, M., and Simon, H. Mesocorticolimbic dopaminergic network: Functional and regulatory roles. Psychol Rev 71(1):155-234, 1991.

McMillen, B.A.; Johns, J.M.; Bass, E.W.; and Means, L.W. Learning and behavior of adult rats exposed to cocaine throughout gestation. Teratology 43:495, 1991.

Meyer, J.S.; Sherlock, J.D.; and MacDonald, N.R. Effects of prenatal cocaine on behavioral responses to a cocaine challenge on postnatal Day 11. Neurotoxicol Teratol 14:183-189, 1992.

Molina, J.C.; Hoffmann, H.; Spear, L.P.; and Spear, N.E. Sensorimotor maturation and alcohol responsiveness in rats prenatally exposed to alcohol during gestational day 8. Neurotoxicol Teratol 9:121-128, 1987.

Molina, V.A.; Wagner, J.M.; and Spear, L.P. The behavioral response to stress is altered in adult rats exposed prenatally to cocaine. Physiol Behav 55:941-945, 1994.

Moody, C.A.; Frambes, N.A.; and Spear, L.P. Psychopharmacological responsiveness to the dopamine agonist quinpirole in normal weanlings and in weanling offspring exposed gestationally to cocaine. Psychopharmacology 108:256-262, 1992.

Nelson, L.R.; Taylor, A.N.; Lewis, J.W.; Branch, B.J.; and Liebeskind, J.C. Prenatal exposure to ethanol alters responding in a "behavioral despair" paradigm. Proc West Pharmacol Soc 27:583-586, 1984.

Nelson, L.R.; Taylor, A.N.; Lewis, J.W.; Poland, R.E.; Redei, E.; and Branch, B.J. Pituitary-adrenal responses to morphine and footshock stress are enhanced following prenatal alcohol exposure. Alcohol Clin Exp Res 10(4):397-402, 1986.

Perez, V.J.; Gonzalez, G.E.; and Smith, C.J. Exposure to ethanol during pregnancy in mice—potential importance of dose for the development of tolerance in offspring. Physiol Behav 30:485-488, 1983.

Peris, J.; Coleman-Hardee, M.; and Millard, W.J. Cocaine in utero enhances the behavioral response to cocaine in adult rats. Pharmacol Biochem Behav 42:509-515, 1992.

Peters, M.A., and Hovious, J.R. Opiate self-administration in adult offspring of opiate-treated female rats. Fed Proc 42:1363, 1983.

Phillips, D.S., and Stainbrook, G.L. Effects of early alcohol exposure upon adult learning ability and taste preferences. Physiol Psychol 4(4):473-475, 1976.

Randall, C.L., and Boggan, W.O. Effects of low-dose prenatal alcohol exposure on behavior and the response to alcohol. Abstract. Alcohol Clin Exp Res 4:226, 1980.

Randall, C.L.; Hughes, S.S.; Williams, C.K.; and Anton, R.F. Effect of prenatal alcohol exposure on consumption of alcohol and alcohol-induced sleep-time in mice. Pharmacol Biochem Behav 18:325-329, 1983.

Rosengarten, H., and Friedhoff, A. Enduring changes in dopamine receptor cells of pups from drug administration to pregnant and nursing rats. Science 203:1133-1135, 1979.

Scalzo, F.M.; Ali, S.F.; Frambes, N.A.; and Spear, L.P. Weanling rats exposed prenatally to cocaine exhibit an increase in striatal D2

dopamine binding associated with an increase in ligand affinity. Pharmacol Biochem Behav 37:371-373, 1990.

Smith, R.F.; Mattran, K.M.; Kurkjian, M.F.; and Kurtz, S.L. Alterations in offspring behavior induced by chronic prenatal cocaine dosing. Neurotoxicol Teratol 11:35-38, 1989.

Sobrian, S.K.; Burton, L.E.; Robinson, N.L.; Ashe, W.K.; James, H.; Stokes, D.L.; and Turner, L.M. Neurobehavioral and immunological effects of prenatal cocaine exposure in the rat. Pharmacol Biochem Behav 35:617-629, 1990.

Spear, L.P., and Scalzo, F.M. Behavioral, psychopharmacological, and neurochemical effects of chronic neuroleptic treatment during development. In: Riley, E.P., and Vorhees, C.V., eds. Handbook of Behavioral Teratology. New York: Plenum Press, 1986. pp. 173-184.

Taylor, A.N.; Branch, B.J.; Kokka, N.; and Poland, R.E. Neonatal and long-term neuroendocrine effects of fetal alcohol exposure. Monogr Neural Sci 9:140-152, 1983.

Taylor, A.N.; Branch, B.J.; Liu, S.H.; and Kokka, N. Long-term effects of fetal ethanol exposure on pituitary-adrenal responses to stress. Pharmacol Biochem Behav 16:585-589, 1982.

Taylor, A.N.; Branch, B.J.; Nelson, L.R.; Lane, L.A.; and Poland, R.E. Prenatal ethanol and ontogeny of pituitary-adrenal responses to ethanol and morphine. Alcohol 3:255-259, 1986.

Van Dijken, H.H.; Van Der Hyden, J.A.M.; Mos, J.; and Tilders, F.J.H. Inescapable footshocks induce progressive and long-lasting behavioral changes in male rats. Physiol Behav 51:787-794, 1992.

Weinberg, J. Hyperresponsiveness to stress: Differential effects of prenatal ethanol on males and females. Alcohol Clin Exp Res 12:647-652, 1988.

Weinberg, J. Prenatal ethanol exposure alters adrenocortical development of offspring. Alcohol Clin Exp Res 13(1):73-83, 1989.

Weinberg, J., and Gallo, P.V. Prenatal ethanol exposure: Pituitary-adrenal activity in pregnant dams and offspring. Neurobehav Toxicol Teratol 4:515-520, 1982.

Weinberg, J.; Nelson, L.R.; and Taylor, A.N. Hormonal effects of fetal alcohol exposure. In: West, J.R., ed. Alcohol and Brain Development. New York: Oxford University Press, 1986. pp. 310-342.

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**Click here to go to page 146**