Postnatal Effects of Prenatal Exposure to Psychoactive Drugs

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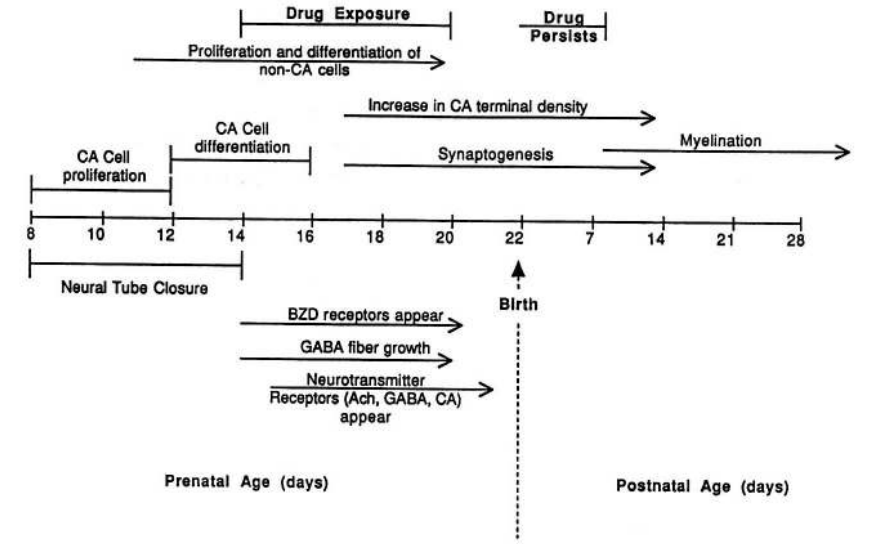
Full Text: Headnote ABSTRACT: Exposure to anxiolytic drugs during the third week of gestation in the rat leaves a lasting imprint on the organism. Functionally, animals exposed prenatally to diazepam (Valium) demonstrate alterations in arousal-attention and stress-related functions. Neural systems underlying these functions are also influenced by the early exposure. The effects of early diazepam exposure are related to the interaction of the drug in utero with specific binding sites in the fetal brain. The consequences of the early exposure, however, often do not become evident until after a period of normal development and become most apparent as the organism reaches young adulthood (late adolescence). These observations suggest that changes that take place in an organism during puberty are necessary for full expression of the effects of prenatal diazepam exposure. Furthermore, the results implicate perinatal insults at the molecular level in the etiology of behavioral disorders that emerge during adolescence. INTRODUCTION The final organization of the nervous system and the behavioral capacity of an organism involve the interaction among three major influences: the genome, the pre- and postnatal chemical environment, and the external environment the organism finds and makes (Oppenheim &Haverkamp, 1986). That neural and functional development can be altered by the external environment has been well established. For example, Harlow showed that the maturation of appropriate species specific behaviors depends upon an appropriate maternal and peer environment (Harlow, Dodsworth, &Harlow, 1965), and Rosenzweig, et al., reported that the quality of the early environment exerts long-term effects on the organization of the nervous system (Rosenzweig, Bennett, &Diamond, 1972). Hubel and Wiesel and others have shown that the organization of sensory systems is profoundly influenced by the nature of early sensory stimuli (Hubel &Wiesel, 1970). The internal chemical environment can also exert marked influences on neural and functional development. For example, early exposure to sex steroids permanently alters the sex bias of a bipotential brain, perhaps through alterations in neuronal gene expression (Toran-Allerand, 1986). Important influences of the internal chemical environment are drugs to which the developing organism may be exposed. Drugs exert their effects on the organism through interaction with specific receptive molecules, as proposed by Langley in the early part of this century (Langley, 1906). Because the central nervous system is a major target for psychoactive drugs, the presence of specific receptors in the developing brain is linked to the developing organism's vulnerability to such drugs. Plasticity is a signature of the developing brain, so exposure to selective drugs over specific developmental periods could influence the continued course of neural development. A specific drug influence on the developing brain will depend on several factors: (1) the presence of specific recognition sites for the drug, (2) the maturational state of effector systems that translate the interaction of a drug with a binding site into a response and (3) the interactions that directly affected neurons have with other neurons and the maturational state of specific neural circuitry. MECHANISM OF ACTION OF BENZODIAZEPINE COMPOUNDS This paper will discuss the consequences of late gestational exposure of rats to the anxiolytic/anticonvulsant benzodiazepine (BZD) compounds. These drugs are thought to act in the brain at a recognition site that is part of an oligomeric complex containing, in addition to the BZD binding site, the recognition site for the inhibitory neurotransmitter γ-aminobutyric acid (GABA), and an associated chloride (Cl-) channel (Schwartz, 1988, Tallman &Gallagher, 1985). This complex is located on the neuronal plasma membrane. Subsets of the polymolecular complex may be defined by differential sensitivity to various BZD compounds (Hebebrand, Friedl, &Propping, 1988). The action of BZDs such as diazepam (Valium) at the complex is to facilitate the action of GABA on the chloride channel.

Stimulation of the movement of Cl- through the Cl- channel leads to inhibitory responses in receptive cells. As the neurotransmitter in 25-45% of all nerve endings (Belin et al., 1980), GABA is the major inhibitory transmitter in the central nervous system. Clearly, alteration in neurotransmission of such a widely distributed system during critical stages of development could be expected to have considerable impact on the developing CNS. Available evidence supports the hypothesis that occupancy of BZD receptors during early stages of development can influence the action of GABA on receptive cells. Receptors to BZD drugs have been identified in the rat brain by the beginning of the third week of gestation (Braestrup &Nielsen, 1978; Schlumpf, Richards, Lichtensteiger, &Mohler, 1983) and in human brain by 12 weeks conceptual age (Aaltonen, Erkkola, &Kanto, 1983; Brooksbank, Atkinson, &Balazs, 1982). Furthermore, we have shown that diazepam (DZ) can facilitate the action of GABA in rat fetal synaptoneurosomal preparations of cerebral cortex by 20 days gestation (Kellogg &Pleger, 1989). In addition to their action on the central-type BZD-GABA complex, BZDs also interact with a site in the brain termed the peripheral-type site, so-named because it was first identified in peripheral organs (Anholt, De Souza, Oster-Granite, &Snyder, 1985; Pazos Cymerman, Brobst, &Palacios, 1986). The peripheral-type BZD binding site is not linked to the GABA receptor. The functional importance of this site is not understood, but its association with mitochondria (Anholt, Peterson, De Souza, &Snyder, 1986; Doble et al., 1987) implies a role in the regulation of cellular metabolism. Indeed, as indicated below, in utero exposure to BZDs does lead to altered cerebral metabolism, implicating the peripheral-type site as a participant in initiating long-term effects of early developmental exposure to BZDs. INTERPRETING EXPERIMENTAL RESULTS When interpreting the results of in utero exposure of experimental animals to psychoactive drugs three facts must be kept in mind, particularly if one wishes to generalize the interpretations to humans. First, the state of maturation of the brain relative to birth varies among different mammalian species. The rat brain at birth is biochemically comparable to a human brain around 20 weeks of gestation (Dobbing, 1974). Nonetheless, the sequencing of specific neural events is similar among species (see Miller, Kellogg, &Saltzman, 1987). Thus, when making comparisons, we consider developmental events taking place during the exposure period rather than the relationship of the exposure period to birth. The relationship between our prenatal exposure period to DZ and developmental events is shown in Fig. 1. second, the rate of clearance of drugs varies among species, i.e., the half-life of bioavailability of a drug is species dependent, so drugs have to be given in markedly different doses to different species in order to achieve a given plasma concentration. Thus, a dose of DZ at 2.5 mg/kg to pregnant rats yields plasma levels of drug and metabolite comparable to those following DZ doses of 10-30 mg during human pregnancy and labor (see Kellogg, 1988). Third, the persistence of a drug in the organism exposed in utero must be established. Some effects observed following prenatal drug exposure may reflect a direct action of persisting drug. For example, the hypotonia and hypothermia observed in newborn human infants exposed to DZ during labor (CreeMeyer, &Hailey, 1975; Owen, Trani, &Blair, 1972) are probably due to a direct action from drug persisting in the neonate. Experimental studies have shown that some drugs, such as methadone, may persist, albeit at low levels, beyond 3 weeks postnatal age following administration of the drug to the pregnant dam (Levitt, Hutchings, Bodnarenko, &Leicach, 1982). Diazepam, however, is immeasurable by 3 weeks of age following prenatal exposure (Simmons, Miller, &Kellogg, 1983). So functional alterations observed beyond that period cannot be due to a direct action of DZ.

Figure 1

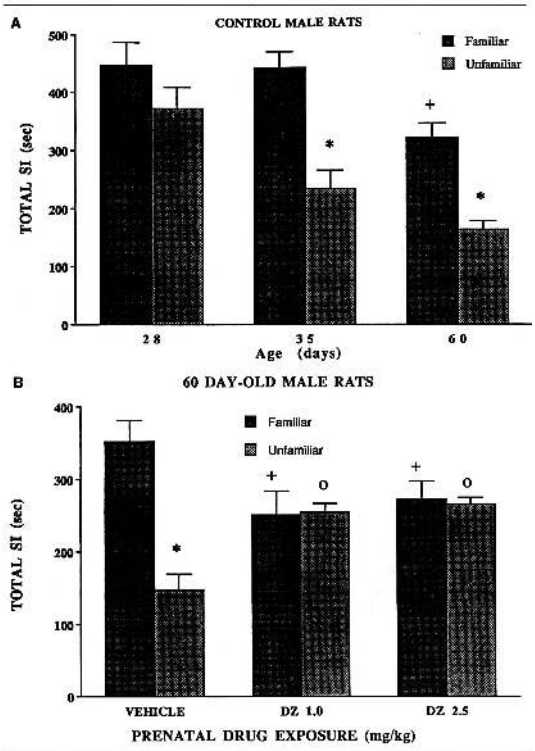


Relationship of the period of prenatal DZ administration to pregnant rats and persistence of the drug in the brains of the progeny to some developmental events in the fetal and neonatal rat brain. Abbreviations: CA=catecholamine, BZD=benzodiazepine, GABA=γ-aminobutyric acid, Ach=acetylcholine.

NEURAL AND FUNCTIONAL CONSEQUENCES OF PRENATAL EXPOSURE OF RATS TO DIAZEPAM AND OTHER BENZODIAZEPINES A review of the literature concerning the effects of perinatal exposure of experimental animals to DZ allows three general conclusions: (1) Consequences of early developmental exposure to DZ reflect interference with arousal-attention and stress-related functions. (2) The consequences become most pronounced when the animals are challenged. (3) The most pronounced effects of the exposure are not expressed until late adolescence or young adulthood, following a prolonged period of normal development. Data supporting each of these conclusions will be presented. Considering that BZDs are anxiolytic and anticonvulsant compounds, one might predict that early developmental exposure to such drugs could interfere with related behaviors. In the rat, the acoustic startle response made to an intense auditory tone burst is markedly potentiated by noise of moderate intensity (Hoffman &Searle, 1965). Potentiation by background noise is presumed to result from activation of an arousal mechanism and, in adult animals, is attenuated by DZ (Sullivan &Kellogg, 1985). Exposure to DZ over gestation days 13-20 interfered with the development of noise potentiation of the acoustic startle response over postnatal days 12-20 (Kellogg et al., 1980). The basal startle response (response in the absence of background noise) was decreased at these ages. Prenatally exposed rats tested as adults, however, demonstrated normal potentiated acoustic startle response, although the basal acoustic startle response remained altered, with the direction of the alteration a function of prenatal exposure dose (Sullivan and Kellogg, 1985; Kellogg, 1988). This initial study demonstrated that early developmental exposure to the anxiolytic compound DZ can alter behaviors that engage underlying arousal mechanisms. Indication that prenatal exposure to DZ can influence arousal/ attention functions has come also from other laboratories. Prenatal exposure of rats to DZ over gestational days 15-20 (at 5-7.5 mg/kg) altered sleep EEG patterns in 4 month-old animals (Livezey, Radulovacki, Isaac, &Marczynski, 1985). The changes in EEG patterns indicated impaired synchronization of neuronal firing. Additionally, one year old cats prenatally exposed to DZ demonstrated depressed post-reinforcement EEG synchronization (Livezey, Marczynski, &Isaac, 1986). Environmental cues, therefore, appear to be processed differently in animals prenatally exposed to DZ. Recently, we have shown that prenatal exposure to DZ alters behavioral indices of anxiety related to social interactions. Anxiety is assessed by examining interactions between two rats (strangers

to each other) placed in an environment that is unfamiliar (but neutral) to both (File, 1985). The amount of time that adult male rats spend in active social interaction is greater in a familiar than in an unfamiliar environment. Furthermore, the amount of time pairs of rats spend in social interaction in an unfamiliar environment is increased by acute exposure to DZ. Environmentally-related social interaction appears with the onset of puberty in male rats (Fig. 2), and juvenile castration prevents the appearance of a differential response to the two environments (Primus &Kellogg, 1989a). Pubertal events also influence the modulation of social interaction in the unfamiliar environment by anxiolytic drugs in that acute DZ is not effective until late adolescence (Primus &Kellogg, In Press). Furthermore, as shown in Fig. 2, prenatal exposure to DZ (1.0 or 2.5 mg/kg over gestational days 14-20) abolishes environment-related differences in social interaction in young adult male rats (Primus &Kellogg, 1989b; Kellogg, Primus and Bitran, Submitted). Therefore, perinatal as well as peripubertal influences are important for the organization of social behaviors related to challenge/anxiety. Prenatal exposure to DZ also alters characteristic physiologic responses to stress (Simmons, Miller, &Kellogg, 1984). Increases in plasma corticosterone (over high basal levels) induced by placing adult rats in restraint stress were attenuated by prenatal exposure to DZ. This effect of DZ was prevented by coexposure to the central-type BZD receptor antagonist, Ro 15-1788 (Flumazenil). Furthermore, prenatal exposure to DZ also altered neural responses to restraint stress. Norepinephrine(NE)-containing neurons that project to the hypothalamus are critically important regulators of the corticosterone response to stress. Whereas two hours of restraint stress induced a significant decrease in NE levels in the hypothalamus of control animals, no decrease was measured in adult prenatally exposed rats. In addition, exposed rats did not demonstrate the stress-induced increase in NE turnover that was observed in control rats. These effects of prenatal DZ exposure on neural stress responses were also prevented by coexposure to the BZD antagonist, suggesting that the effects of the exposure on these classic stress responses were mediated by action of the drug in utero at the central-type BZD receptor complex. It might be hypothesized that since prenatal DZ exposure interferes with what has been defined as the 'classic' stress response (Selye, 1973), then the influence of the early exposure on stress-related behaviors results from this interference. However, work from this laboratory indicates that physiologic and behavioral responses to stressors develop independently and under different influences. Thus, an unfamiliar environment can stimulate the corticosterone response to stress in prepubertal rats (Guillet and Kellogg, 1988). However, an unfamiliar environment does not influence social interaction until after the onset of puberty (Primus &Kellogg, 1989a). Furthermore, while juvenile castration abolished the impact of the unfamiliar environment on social interaction in adult male rats, it did not alter the corticosterone response to an unfamiliar environment. Because early exposure to DZ altered both hormonal and behavioral responses to challenge in the young adult rat, the effect of the early drug exposure appears to involve different levels of neural organization.

Figure 2

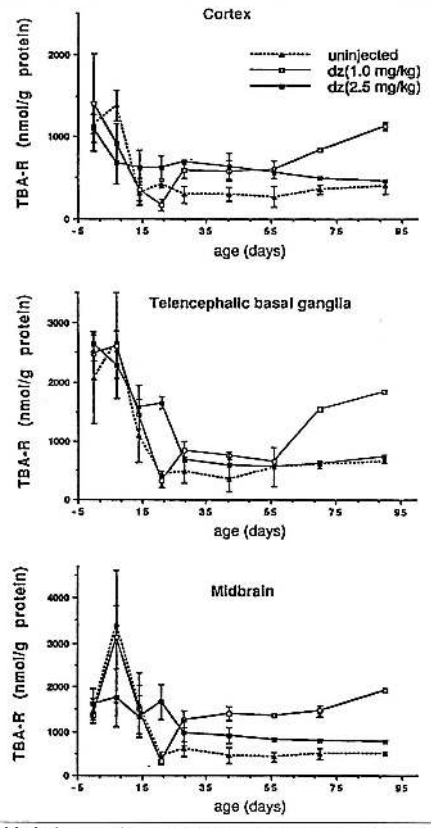


The effect of environment (familiar vs unfamiliar) on social interaction (SI) in pairs of male rats. A: SI as a function of pubertal age (onset of puberty in the male rat is 30-32 days of age). From Primus and Kellogg, 1989a. B: SI in 60 day-old rats as a function of prenatal exposure (over gestational days 14-20) to DZ (1.0 or 2.5 mg/kg/day) or vehicle. From Primus and Kellogg, 1989b. * indicates significant difference in SI between familiar and unfamiliar environments for a respective group. + indicates significant difference from days 28 and 35, familiar environment only (A) and significant difference from vehicle-exposed, familiar environment (B). O indicates significant difference from vehicle group, unfamiliar environment.

As indicated above, the effects of prenatal exposure to DZ are most readily expressed when the organism is challenged. If the exposure alters arousal, anxiety and stress-related functions, then the need to challenge the organism in order for the effects of the exposure to be observed may seem quite logical. The effects of prenatal exposure to DZ have been observed, however, in tests not directed at measurement of stress-related or anxiety-related behaviors but that do involve a challenge. For example, Grimm and collaborators have observed that perinatal exposure to DZ (5 or 10 mg/kg) impairs acquisition and retention of a complex discrimination task that requires the animal to attend simultaneously to more than one aspect of the stimulus situation (Gai &Grimm, 1982; Frieder, Epstein, &Grimm, 1984). The prenatal exposure did not affect performance in a simple maze paradigm that did not involve simultaneously presented stimuli, nor did it affect motor learning. Although DZ exposure certainly induces changes in neurotransmitter function in brain regions that may be functionally related to learning (Frieder &Grimm, 1985), the behavioral changes may also reflect other drug effects. Prenatal exposure to DZ induces changes in cellular energy metabolism associated with action of the drug in utero at both central- and peripheral-type BZD receptors (Miranda, Ceckler, Guillet, &Kellogg, 1990). The fact that the effects of the early exposure become most pronounced when the organism is challenged may indicate that the interference with cellular metabolism limits the organism's ability to meet metabolic demands. The observation that the primary effects of early DZ exposure do not become apparent until the organism approaches maturity is of particular importance to our understanding of how developmental exposure to DZ may influence the organism. This observation is also of importance in generalizing the significance of the experimental findings because many clinical behavioral disorders have their onset after puberty (Campbell &Spenser, 1988). A change in the chemical environment of specific developing receptor systems may interact with specific, genetically mediated events to trigger a cascade of events that lead to later behavioral disorders. Delayed expression of the effects of early DZ exposure has been observed at the cellular, neural systems, and

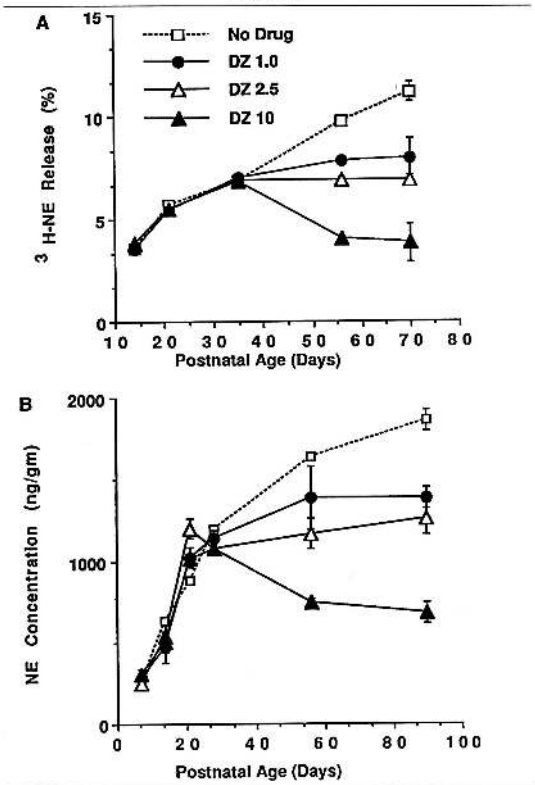
behavioral level. At the cellular level, prenatal exposure to DZ and related compounds dramatically increased brain levels of cytotoxic aldehydes in 3 month-old animals. Levels of cytotoxic aldehydes (Fig. 3) are normally high at birth and decrease to control adult levels by 3 weeks of age (Miranda, Wagner, &Kellogg, 1989). This developmental profile was similar in rats prenatally exposed to DZ, but after 8 weeks of age the level of cytotoxic aldehydes increased in prenatally exposed animals relative to controls. The early DZ exposure may have interfered with specific metabolic processes that perhaps are recruited with the establishment of sexual maturity. At the neural systems level, the effects of early DZ exposure on the NE projection to the hypothalamus (see Fig. 4) were not apparent until after 5 weeks of age (Simmons, Kellogg, &Miller, 1984; Kellogg &Retell, 1986). In contrast to the NE projection to the cerebral cortex, functional activity within the hypothalamic NE system is normally delayed, and the NE turnover rate in the hypothalamus of control rats at 4 weeks of age is only one-third that of the rate measured in 10 week-old young adult rats (Kellogg &Wennerstrom, 1974; Simmons, Kellogg, &Miller, 1984). These normal maturational changes that take place after the onset of puberty (around 30-35 days) appear to involve factors influenced by prenatal DZ exposure.

Figure 3



Levels of thiobarbituric acid-reactive (TBA-R) material in 3 brain regions measured from birth (day 0) to 90 days of age in uninjected control rats or following *in utero* exposure (over days 14–20) to DZ (1.0 or 2.5 mg/kg/day). TBA-reactive material is a measure of cytotoxic aldehydes. From Miranda, Wagner, and Kellogg, 1989).

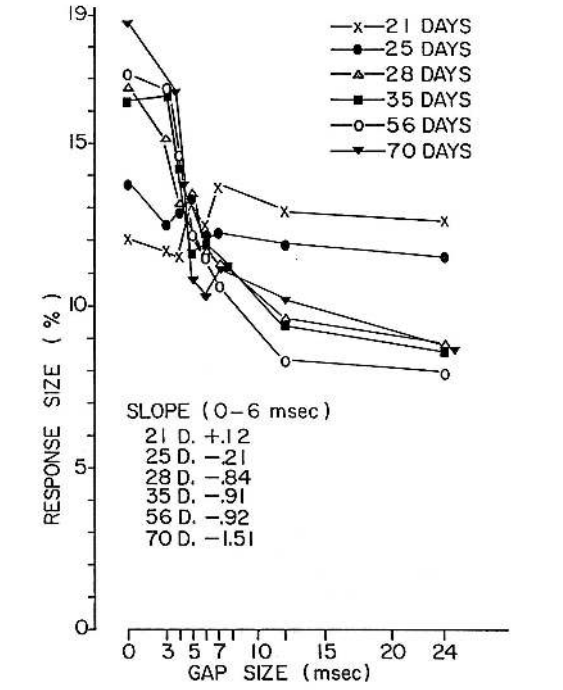
Figure 4



Developmental time-course of hypothalamic NE projections. A: Changes in depolarized release of ^{3}H-norepinephrine (NE), induced by incubation in 25 mM potassium, from isolated rat hypothalamus as a function of postnatal age and prenatal exposure to DZ (1.0, 2.5, or 10.0 mg/kg/day) or vehicle (No Drug) over gestational days 13–20. From Kellogg and Ketell, 1986. B: Changes in NE concentration in the hypothalamus of rats as a function of postnatal age and prenatal exposure to DZ or vehicle. Prenatal exposure levels same as for Fig. 4A. From Simmons, Kellogg, and Miller, 1984.

Several behavioral studies have illustrated the delay in the expression of the effects of prenatal exposure to DZ. As observed with the effects on the hypothalamic NE projection, the behavioral manifestations become apparent at a time when there is a normal transition in the function. For example, prenatal DZ exposure alters the maturation of temporal acuity in the auditory system (Kellogg, Ison, &Miller, 1983). Acuity was defined by the effectiveness of brief (3-24 msec) silent periods (gaps) in white noise to inhibit the acoustic startle reflex (Ison, 1982). Studies in humans have shown that individual differences in auditory temporal acuity are related to speech perception in adults (Trinder, 1979) and to language and learning disabilities in children (McCrosky &Kidder, 1980). In untreated rats, gaps become effective in inhibiting the acoustic startle response between 25 and 28 days of age (Kellogg, Ison, &Miller, 1983). Sensitivity to the silent periods is stable from 28 through 56 days of age. But at 70 days there is an increase in sensitivity to the inhibitory effect of the gaps. The developmental profile in control rats, shown in Fig. 5, occurs over a developmental period comparable to that over which auditory temporal resolution improves in children (Davis &McCrosky, 1980). Other than a developmental delay (from 28 to 35 days) in the onset of gap detection in animals exposed prenatally to a high dose of DZ (10 mg.kg), no effect of the early exposure was observed until the animals reached 70 days. At this age, prenatally exposed animals showed both altered sensitivity to gap detection and altered inhibition at gaps of long duration (Kellogg, Ison, &Miller, 1983). Hence, as the animals reached the age when a normal change in sensitivity takes place, the effects of the prenatal exposure become expressed. All of these observations suggest that exposure to DZ at particular developmental periods interferes with the organization of specific neural mechanisms and/or systems involved in mediating arousal/anxiety and stress-related behaviors, behaviors whose adult expression is influenced by the events of puberty.

Figure 5



Development of auditory temporal acuity in rats. The response at each gap size was averaged across 8 trials and then normalized by dividing each response by the total sum of the responses. The response at any gap duration, therefore, represents a percentage of the total response. Increasing inhibition of the acoustic startle response by increasingly larger gaps in background noise will result in an increased proportion of the total response being present in the control (0 gap) trial. The slope of the response curve measured over gaps up to six ms in duration provides an index of sensitivity to the interrupted noise. As can be seen, marked changes in sensitivity to gap detection (temporal acuity) occur between 25 and 28 days of age and between 56 and 70 days. It is at 70 days that alterations in gap detection are noted following prenatal exposure to DZ. From Kellogg, Ison, and Miller, 1983.

HOW DO BENZODIAZEPINES INFLUENCE THE DEVELOPING BRAIN AT THE TIME OF EXPOSURE?

While it is not yet clear just how BZD compounds influence the brain during the time of exposure, the long-term consequences of early developmental exposure to these drugs suggest that the drugs influence the organization of specific cellular functions and systems. In vitro exposure of fetal rat neuronal cell cultures to DZ decreases the uptake of 2-deoxyglucose, an indication that neural activity was decreased by the exposure (Daval, De Vasconcelos, &Lartaud, 1988). This observation is consistent with the observation that DZ facilitates the action of GABA on the chloride channel in fetal brain tissue (Kellogg &Pleger, 1989). GABA may exert trophic (growth promoting) influences on neural development (Wolff, 1981; Madtes, 1987). Early exposure to BZD compounds could, therefore, alter this influence of GABA. Diazepam reportedly alters neuronal fiber outgrowth in fetal rat neuronal cell cultures (Duval, De Vasconcelos, &Lartaud, 1988), and peripheraltype BZDs influence neurite outgrowth in cells of neural tumor origin (Morgan et al., 1985). Benzodiazepines that act at peripheral type BZD receptors have also been shown to inhibit cell proliferation (Wang, Morgan, &Spector, 1984) and to stimulate the expression of an oncogene product related to cell proliferation and survival (Curran &Morgan, 1985). Through such mechanisms, early developmental exposure to BZDs could cause enduring changes in cell function. Changes in the characteristics of the receptor itself are likely changes in cell function related to early occupancy of a receptor by a drug. In utero exposure to neuroleptic compounds produces a decrease in receptor density in specific brain regions (Friedhoff &Miller, 1983). On the other hand, prenatal exposure to BZD compounds does not lead to a reliable or consistent change in BZD receptor density or affinity for BZD drugs (Kellogg, 1988). However, an influence on receptor function can be expressed in other ways, such as changing effector mechanisms and responsiveness. We have shown that prenatal exposure to DZ increases the sensitivity of the BZD-GABA-C1- channel complex in adult cerebral cortex preparations to GABA (Primus and Kellogg, 1989b; Kellogg, Primus, &Bitran, Submitted). This means the complex in exposed animals

is tuned to be more responsive to low concentrations of GABA, an effect that in normal, untreated animals is brought about by acute administration of BZDs. This enhanced sensitivity to GABA could account in part for the observation that prenatally exposed animals often behave as through they had been acutely administered DZ. Recall that, in the social interaction test for anxiety, prenatally exposed adult male rats do not demonstrate a differential environmental response, as is also observed when control rats are administered DZ acutely. This change in functioning at the BZD-GABA-Cl^sup -^ channel complex could also account in part for the observation that prenatal exposure to DZ alters behavioral responses to specific environmental cues. As indicated above, psychoactive drugs, such as DZ, interact with specific binding sites that tend to have specific, non-uniform distribution patterns in the brain. Therefore, if certain cues activate specific neural circuitry, then the behaviors related to activity in that circuitry could be altered if the function of selective receptors in the circuitry has been influenced by early developmental drug exposure. Early receptor occupancy by drugs could also influence the organization of specific neural circuits such that environmental cues do not activate appropriate neural circuits following early drug exposure. Finally, enduring changes in cell function brought about by early DZ exposure may alter the neurotransmitter profile of specific neurons. We now know that two or more neurotransmitters often coexist in the same neuron (Hokfelt et al., 1986). In particular, neuropeptides have been observed to share residence with many of the classically accepted transmitters. Furthermore, specific neuropeptides may reside in a neuron only at certain developmental stages, and the expression of a particular peptide in a given neuron may be dependent upon the environment of that neuron (Schultzberg et al., 1986). Hence, a change in the internal chemical environment brought about by the presence of a drug during development may influence the neurotransmitter profile of selective neuronal populations. That effects of late gestational exposure of rats to DZ become most apparent after the onset of puberty suggests that the mechanisms or systems altered by the in utero exposure undergo a change during adolescence. Our studies, reported above, certainly have indicated that many of the measures altered by prenatal DZ exposure normally undergo a change over the period of adolescence (see above). Furthermore, our studies have shown that intact gonadal function is critical for the emergence of mature adaptive behavioral responses. The timely appearance during puberty of behavioral responses to challenge may reflect an organization of behavior that benefits the survival and reproductive success of an organism. That prenatal DZ exposure interferes with pubertal development of both neural and behavioral responses to challenges emphasizes the importance of pubertal events (such as gonadal hormone secretion) in the expression of the effects of early DZ exposure. SUMMARY Studies of prenatal DZ exposure in experimental animals should assist in the focussing of investigations in humans. Those working with human adolescents should look at pre- and perinatal insults at the molecular level as a causative factor of behavioral disorders that emerge with adolescence. Because of early insults, appropriate neural changes that should normally take place during adolescence may not occur, thereby interfering with the acquisition of mature behaviors. In support of this suggestion, an influence of prenatal alcohol exposure in the development of schizophrenia almost two decades after birth has been suggested (Lohr &Bracha, 1989). In addition to BZDs, barbiturates, alcohols, volatile anesthetics, and synthetic and natural steroids have been shown to influence function of the BZD-GABA receptor complex (Schwartz, 1988). The sensitivity of this complex, which appears to play a major role in neural organization, to such a spectrum of chemical agents makes this complex a vulnerable site through which neural and behavioral development may be influenced. References REFERENCES Aaltonen, L., Erkkola, R. &Kanto, J. (1983). Benzodiazepine receptors in the human fetus. Biol. Neonate 44, 54-57. Anholt, R.R.H., De Souza, E.B., Oster-Granite, M.L. &Snyder, S.H. (1985). Peripheral type benzodiazepine receptors: Autoradiographic localization in whole-body sections of neonatal rats. Journal of Pharmacology and Experimental Therapeutics 233, 517-526. Anholt, R.R.H., Peterson, P.L. De Souza, E.B. &Snyder, S.H. (1986). The peripheral benzodiazepine receptor: Localization to mitochondrial membranes. Journal Biologic Chemistry 261, 576-583. Belin, M.F., Gamrani, H., Agnera, M., Calas, A. &Pujol, J.F. (1980). Selective uptake of [^sup 3^H]gammaaminobutyrate by rat supra- and

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