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THE EFFECT OF NICOTINE ON DEVELOPING BRAIN CATECHOLAMINE SYSTEMS

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1. ABSTRACT

Biochemical studies have confirmed that nicotinic acetylcholine receptor mRNA and protein are expressed early in the development of the fetal central nervous system. Perinatal administration of nicotine produces a broad spectrum of effects on brain development, including inhibition of DNA synthesis, altered ornithine decarboxylase activity, altered neurotransmitter function, and significant alterations in cortical morphogenesis. Catecholamine systems, both in the brain and in the periphery, are particularly sensitive to prenatal nicotine exposure. Acute and chronic nicotine administered to pregnant dams causes alterations in dopamine and its metabolites in male and female rat fetuses. These changes can persist into adulthood. Prenatal nicotine exposure also causes locomotor disturbances in pups, which can have long-lasting effects. The effect of nicotine on developing noradrenergic neurons is less clear. Some effects may include increases in noradrenergic neuronal activity in the pup and aberrant central release of norepinephrine in response to neonatal hypoxia after nicotine exposure *in utero*. Catecholamine neurons develop early in ontogeny, so nicotine induced alterations have the potential to induce permanent changes. Hence, more research is needed to get a clearer picture of the effect of nicotine on developing catecholamine systems. The affects of nicotine on catecholamine systems in the adult are discussed for comparison.

2. INTRODUCTION

As the incidence of cigarette use among teenage girls and young women increases (1,2), the consequences of maternal smoking on fetal outcome increase in clinical significance. Maternal cigarette smoking during pregnancy is highly correlated with a number of adverse outcomes in their offspring. An overall growth retardation is the most obvious consequence of prenatal cigarette exposure. Neurobehavioral disturbances, which manifest as learning

disabilities, cognitive deficits and hyperactivity (resulting in a syndrome similar to attention-deficit hyperactivity disorder-ADHD) are often the most lasting reminders of tobacco toxicity (3-5). Epidemiological data show that maternal smoking is a major risk factor for sudden infant death syndrome (SIDS) (6,7) with maternal smoking leading to increased perinatal mortality (reviewed by Behnke & Eyler, 1993 (8)). While there are many potentially dangerous compounds in tobacco smoke, nicotine has been found to be one of the principal neurotoxins (9). Nicotine readily crosses the blood brain barrier (10) and is secreted into breast milk (11). Other components in cigarette smoke, such as carbon monoxide and cyanide, may induce nutritional deficits and hypoxia in the maternal-fetal unit which may result in indirect changes in brain growth and development (12).

Evidence for interaction between nicotine and catecholamines abounds in the scientific literature of the last 20 years. Tremendous progress has been made using molecular, cellular and system approaches to understand nicotine's effect on the brain and on a myriad of human diseases. This paper will review nicotine's effects on brain catecholamine systems, with a specific emphasis on this alkaloid's unique consequences in the developing brain.

3. REVIEW OF CATECHOLAMINE SYSTEMS IN THE BRAIN

3.1. Introduction to Brain Catecholamine Systems

Dopaminergic, noradrenergic, and adrenergic cell groups form the primary catecholaminergic (CA) innervation of the central nervous system (CNS). The cells of each of these neurotransmitter systems arise from relatively small, compact nuclei in vertebrates. These were extensively described by Dahlstrom and Fuxe (13) who classified them into 14 groups, specified A1 to A14, from caudal to rostral. Subsequently, these were updated and extended by Hokfelt *et al*.(14,15), such that six major groups of catecholamine cells are now recognized in the CNS of vertebrates. While somewhat more dispersed in primates, the general anatomical distribution remains highly recognizable.

3.2. Overview of Dopaminergic Systems

The vast majority of dopaminergic cells arise from the midbrain, although some also arise from the diencephalon. The midbrain dopaminergic neurons of the substantia nigra pars compacta (SNC, A9 dopaminergic cell group), and the ventral tegmental area (VTA, A8 dopaminergic cell group) provide substantial dopaminergic inputs to the cortex, caudate-putamen, nucleus accumbens, amygdala, and septum (16). The diencephalic DA group is located within the arcuate nucleus of the hypothalamus. It projects to the pituitary where it regulates the release of various pituitary hormones. Primary functions of the nigrostriatal pathway include sensorimotor integration and control of motor output. Whereas the mesoaccumbal and mesocortical projections are also involved with sensorimotor integration, the processing involves higher order motivational and emotional states rather than proprioceptive information (17). Lesioning of the different dopaminergic projections induce differing behavioral syndromes depending upon the neuronal system lesioned. For example, dopaminergic lesioning of the prefrontal cortex leads to cognitive dysfunctions, dopamine depletion of the mesoseptal dopaminergic projections leads to a decrease in working memory (18), and lesioning of the mesoaccumbens dopaminergic projections cause attention deficit and alterations in locomotor activity (19-21). These findings give insight to dopamine's key role in schizophrenia, Parkinson's disease, Huntington's chorea, manic-depressive illness, and tardive dyskinesia. Dopamine is also involved in reinforcement, generation of pleasure, development of drug addiction, and so forth (16).

3.3. Overview of Noradrenergic System

The primary sources of noradrenergic cells are found more caudal, in brainstem areas. The noradrenergic cell group of the locus coeruleus (LC), the A6 cell group, is thought to be one of the most conserved cell groups of the brain, being preserved in all vertebrate species (22). Located in the rostral pons, it projects widely throughout the neuraxis. Smaller collections of NE neurons are located in the lateral tegmental system and caudal pons. More recent anatomical studies suggest a greater degree of specificity and topographical organization of the LC/NE system than has been previously appreciated (23). The LC provides immense noradrenergic inputs to the neocortex, hippocampus, thalamus, septum, cerebellum and brain stem. Interestingly, the striatum is nearly devoid of any NE innervation (24). NE from the LC is important for attention, arousal, learning, Parkinson's disease, Alzheimer's disease, attention deficit disorder/hyperactivity, post-traumatic stress disorder, hypothalamic function and so forth. The adrenergic cells have a much more limited distribution, but are found in close association with noradrenergic cells of the lateral tegmental system and the dorsal medulla, and project to the hypothalamus, brainstem and spinal cord. Much less is understood about the role of the central adrenergic system, but it appears to be involved in neuroendocrine mechanisms and regulation of blood pressure. We will focus our attention on the DA and NE systems, since little is known regarding the central adrenergic system during development.

3.4. Comparison of Dopaminergic and Noradrenergic Systems

DA and NE are similar in a variety of ways. In both the DA and NE systems there are small numbers of cells projecting to diffuse brain areas. However, the NE projections are more diffuse. This pattern of broad efferent targets suggests a global function for these neurotransmitters since they exert modulatory influences over diverse regions. Indeed, both systems have *en passant* synapses as well as the classic point to point type. DA and NE systems are also similar in that both use reuptake mechanisms as their primary mode of termination of neurotransmitter activity, and their receptors are members of the G-protein coupled family. To generalize, it seems that these CA systems set the basic tone in regions of innervation by modulating the excitable state.

Cells from both systems develop very early in ontogeny. Indeed, DA and NE afferents are the first

neuromodulatory fibers to arrive at the developing neocortex (25). As such, catecholamines may play an important role during brain development because alterations of neurotransmitter levels in fetal brain may induce permanent changes in behavior during adulthood (26). Administering pregnant rats with drugs that affect DA or NE transmission may induce modifications in DA or NE synthesis in the fetal brain (26,27). Drugs that effect neurotransmission may effect the developmental time course of the catecholamines systems (28,29). This is important because catecholamines may modulate neuronal outgrowth and influence the morphology of neuronal architecture (30). Hence, nicotine's effect on the developing brain, as well as the effect on adult brain, will be reviewed.

4. NICOTINIC REGULATION OF CATECHOLAMINES

4.1. Nicotinic Receptor Pharmacology

Nicotine is an exogenous ligand for one of the primary neurotransmitter receptors in the body, the nicotinic cholinergic receptor (nAChR). The nAChR is a ligand-gated ion channel found at the neuromuscular junction (NMJ), within peripheral ganglia, and in the central nervous system (CNS). The receptor consists of five subunits, which vary, in their identity. At the NMJ the nAChR is comprised of 2 alphas, 1 beta, 1 gamma (eplison replaces gamma in the mature animal) and 1 delta subunit. In the CNS they appear to be made up solely of alpha and beta subunits distinct from those found at the NMJ. Studies have identified numerous genes encoding subunits for the nAchR such that 8 alpha subunits (alpha2- alpha9) have been shown to exist, as well as 3 beta subunits (beta2-beta4) (31-33). Experiments using various heterologous expression systems have revealed that the pentameric subunit configuration of the neuronal nAChR usually consists of two alpha and three beta subunits, although five alpha subunits may function as a homomer (34,35). Different subunit combinations yield receptors with differing pharmacological and electrophysiological response profiles, providing a multitude of receptor subtypes (36,37). Recently, anatomical analysis identifying the subunit composition of nAChRs has revealed that subunit expression is developmentally regulated in a distinct pattern (38).

Although heterologous recombination studies may suggest potentially large nAChR heterogeneity, it is important to confirm such findings in native receptor systems. In the rat CNS there is a widespread, but discrete, distribution of nAChR subunit mRNAs and protein (39-44). Each subunit exhibits a unique pattern of localization, with many areas of overlap. Immunoprecipitation studies have indicated that an alpha4/beta2 subunit combination represents the majority of high affinity [^{3}H]nicotine and [^{3}H]cytisine binding sites in rat and chick brain (45,46). However, other subunit combinations are possible (47). An increasing body of functional data, both electrophysiological (48,49) and otherwise (50-52) indicates that there is considerable diversity of central nAChRs. However, much more work is required to correlate the subunit expression within a single cell and the corresponding nAChR properties. Indeed, evidence from studies of peripheral ganglia (53) and central neurons (54) suggests that alternative subunit combinations may be differentially trafficked to yield multiple nAChR subtypes within the same cell.

4.2. Cellular Adaptation to Nicotine

nAChRs are associated with a number of neuronal cell types in the mammalian nervous system (32). In adult tissue, nAChRs are present presynaptically on the nerve terminals of largely excitatory neurons. When activated by the endogenous ligand acetylcholine (Ach), or nicotine, or other cholinergic agonists, nAChRs stimulate the release of acetylcholine, dopamine, noradrenaline and serotonin, with variable efficacy depending on which cell type is being examined (50). However, when stimulated by nicotine rather than Ach, these receptors are activated in a more persistent manner, due to the lack of a timely inactivation mechanism. While metabolism does occur, it proceeds at a relatively slow rate. Even a single exposure to nicotine, while not considered chronic will act on the receptor on a much longer time scale than Ach. A single systemic injection of nicotine can induce mRNA upregulation of the rate-limiting enzyme, tyrosine hydroxylase in the rat locus coeruleus, and subsequently increase nicotine-stimulated NE release up to 4 weeks later (55). This evidence makes it difficult to assign acute vs. chronic nicotine effects because many studies have not allowed adequate time to elapse to fully characterize the effect of acute nicotine exposure. In contrast to Ach, since nicotine is not rapidly inactivated, its effect at the receptor can be considered somewhat persistent and subsequent phenomena may reflect an adaptive response by the cells.

5. NICOTINIC REGULATION OF CATECHOLAMINES IN THE ADULT BRAIN

5.1. Dopamine and Nicotine Interactions

In the adult rat, DA neurons of the substantia nigra/ventral tegmental area (SN/VTA) express mRNA for a number of different nAChR subunits including alpha3, alpha4, alpha5, alpha7, and beta2 (39,40,42,56). High affinity [^{3}H]nicotine binding sites are also localized in this cell body region and in corresponding terminal fields, and are decreased by 6-OHDA lesions (57). Both electrophysiological (58,59) and neurotransmitter release data (60,61) have confirmed the presence of excitatory nAChRs on mesolimbic and nigrostriatal DA cell bodies and terminals. The receptors modulating DA release from these cells have been extensively characterized pharmacologically (51,62-65), and have been shown to be sensitive to antagonism by neuronal bungarotoxin (nBTX) and to desensitize rapidly. Although there is a general consensus that these nAChRs contain nBTX-sensitive alpha3 subunits in combination with beta2 (51,66), their high affinity for [^{3}H]nicotine and response to chronic nicotine exposure suggest that other subunits may be included in their pentameric assembly.

Nicotine can significantly stimulate brain DA release in the mesolimbic system (67-70), the nigrostriatal

system (71,72) and the mesocortical system (73) as measured by *in vivo* microdialysis. Nicotine can stimulate dopamine release from nigrostriatal terminals in the caudate-putamen, and from mesolimbic terminals in the nucleus accumbens as demonstrated by *in vitro* neurotransmitter release assays using brain slices (60,61). Nicotine can also stimulate dopamine release by acting on presynaptic nACh receptors on striatal nerve terminals as demonstrated with striatal synaptosomes (62,63,74). However, systemic nicotine administration can induce DA release to a greater degree in the nucleus accumbens than in the dorsal striatum (75). Intracellular recordings made from cells in the VTA indicate a direct action of nicotine on these DA-containing neurons, thereby providing evidence for the positive reinforcement associated with nicotine consumption (58). Most recently, Picciotto *et al*. (76) used patch-clamp recording to demonstrate that the beta2 subunit of the nAChR is necessary for nicotine stimulated striatal DA release and in beta2 knock-out mice, self-administration of nicotine was attenuated. Thus, the beta2-containing nAChR may be involved in mediating the reinforcing properties of nicotine.

5.2. Dopamine and Nicotine Interactions: Locomotion

Nicotine's action on the mesolimbic dopamine pathway produces enhanced locomotor activity. Dopamine applied to the nucleus accumbens produced a dose-dependent increase in locomotion, which could be blocked by dopamine antagonists (77,78). In addition, injection of nicotine or nicotinic agonists into the VTA or the nucleus accumbens can cause hyperlocomotion (79,80), which can be suppressed by dopamine antagonists (80). Chronic subcutaneous nicotine treatment has been shown to potentiate the locomotor response of other dopaminergic drugs (i.e. amphetamine and apomorphine), indicating that nicotine stimulation augments dopaminergic activity (81). Further, the locomotor stimulant effects of nicotine can be abolished after dopamine depletion by 6-0HDA lesion of the mesolimbic dopamine system (82).

Chronic nicotine treatments can induce different behavioral and biochemical changes, depending on whether the drug is administered continuously or intermittently. Whereas continuous exposure leads to tolerance or reduced drug efficacy (83) intermittent exposure leads to a sensitization to some of nicotine's behavioral effects, including locomotor activity (69,84,85) and drug-seeking behavior (86). This behavioral sensitization, resulting from adaptive changes within the brain, is believed to underlie chronic smoking behavior. Chronic intermittent nicotine pretreatment results in increased nicotine-induced release of dopamine in the medial prefrontal cortex (69,87) and from striatal afferents (50,85,86). However, other studies have reported no enhanced release from striatal afferents (67,69,88). A number of factors may underlie the inconsistency of literature findings on this issue, with mode of drug treatment perhaps being particularly important.

5.3.Dopamine and Nicotine Interactions: Reinforcement

Nicotine is a positive reinforcer, as clearly evidenced by self-administration models. Intravenous nicotine self-administration has been demonstrated in rats, dogs, squirrel monkeys and humans (89-91). Intermittent rather than continuous delivery causes higher rates of lever-pressing in rats and often the lever-pressing continues until toxic effects are experienced (89). Intravenous self-administration of nicotine can be attenuated by nicotinic antagonists mecamylamine (centrally and peripherally acting) and chlorisondamine (centrally acting due to intraventricular injection and poor diffusion across the blood brain barrier), but not by hexamethonium (peripherally acting) (92-94). This gives evidence that the reinforcing effects of nicotine result from action within the central nervous system, not periphery. Moreover, motor impairment did not occur in any of the experiments, thus, the animals were capable of continued lever-pressing if desired. Voluntary nicotine self-administration was reduced by both subtype-selective dopamine antagonists, and 6-OHDA lesions of the ascending mesolimbic projections from the VTA (94,95). This provides further evidence that reinforcement depends at least in part on mesolimbic dopamine.

5.4. Dopamine, Nicotine, and Glutamate Interactions

Nicotine induced c-fos expression can be blocked by both D1 receptor and N-methyl-D-aspartate (NMDA) receptor blockade, suggesting a convergence of dopamine and glutamate systems in mediating some of nicotine's acute actions (96). Furthermore, NMDA receptor antagonists also block locomotor and mesolimbic sensitization induced by chronic, intermittent exposure to nicotine (86,97), implicating glutamate systems in these effects. Thus, a complex picture is emerging. McGehee *et al*. (98) found that *in vitro* intracellular recordings indicate that nicotine acts largely through an indirect, presynaptic mechanism. Moreover, it has been suggested that nicotine-induced increases in nigrostriatal terminal excitability is not a direct effect of nicotine on dopaminergic axons. Rather, nicotine is stimulating glutamate release which activates glutamate heteroreceptors on dopamine-containing terminals (99). In support of this finding, nicotine has been shown to simultaneously increase striatal dopamine and glutamate (73) and a NMDA receptor antagonist can significantly reduce nicotine-induced dopamine overflow (73). Recently, Schilström *et al*. (100) demonstrated that DA release in the nucleus accumbens induced by systemic or intrategmental nicotine is dependent to a significant extent on concomitant stimulation of NMDA receptors in the VTA. These observations suggest that nicotine's responses are mediated to some extent by activation of NMDA receptors.

5.5. Norepinephrine and Nicotine Interactions

In contrast to the clear role of nAChRs in regulating midbrain DA neurons in adult rodent brain, there has been considerable controversy as to nAChR control of NE release. In rat, the locus coeruleus (LC) provides the majority of forebrain NE innervation (24,101), and expresses mRNA for a number of nAChR subunits. However, autoradiographic studies have indicated little labeling of this brain region by high affinity ligands such as [^{3}H] nicotine or [^{3}H]cytisine (102-104). Early *in vitro* neurotransmitter release studies suggested that nicotine-stimulated NE release was not sensitive to calcium, and might therefore be mediated by a non-specific mechanism (59,105).

Furthermore, initial ionotophoretic studies failed to detect a direct nicotine-induced activation of LC (106), and an indirect activation model has been proposed (107). In contrast, intracellular recording of *in vitro* brain slices (1080 and *in vivo* microdialysis (109) have revealed direct nicotinic activation of LC cells. Furthermore, calcium-sensitive nicotine stimulation of NE release from hypothalamic synaptosomes (110), hippocampal slices (52) and hippocampal synaptosomes (111) has been identified. In the latter two studies, both direct and indirect effects of nicotine on hippocampal NE release have been characterized. The pharmacology of the nAChRs involved in NE release appears to be quite distinct from that of nAChRs on striatal DA terminals.

5.6. Norepinephrine and Nicotine Interactions: Stress Response

Various physiological effects of nicotine have been attributed to central activation of the hypothalamic–pituitary–adrenal axis via brainstem nuclei containing CA neurons. Nicotine is a potent stimulus for secretion of the stress-responsive hormones, adrenocorticotropin (ACTH) and prolactin. The effects of a variety of stressors—cold, ether and systemic hypotension—depend to some extent on activation of brainstem NE/E afferents which indirectly release ACTH (112). Nicotinic stimulation of brainstem CA cells leads to the release of prolactin and ACTH from the anterior pituitary via neuronal projections to the paraventricular nucleus (PVN) of the hypothalamus (112). However it is not entirely clear to what extent epinephrine, norepinephrine, or both are responsible for the hormonal release. Administration of epinephrine or norepinephrine directly into the hypothalamus leads to prolactin secretion, with epinephrine exhibiting significantly greater potency (113,114). Using *in vivo* microdialysis, it has been shown that nicotine or nicotinic agonists administered into the fourth ventricle stimulate norepinephrine secretion in the paraventricular nucleus (PVN) of the hypothalamus (115). The resulting release of NE in the PVN, could lead to the release of ACTH secretagogues because the PVN is the site of corticotropin-releasing hormone (CRH) neurons involved in initiating ACTH secretion. Further support for a CA brainstem-mediated effect in the PVN and subsequent ACTH release can be seen in regional examination of nicotine-induced c-fos mRNA expression. Valentine *et al*. (116) have shown that the level of nicotine-induced c-fos expression is dose-dependent in the PVN, LC, and nucleus tractus solitarius (NTS), but that nicotine has greater potency in the NTS and the CRH region of the PVN. Fu *et al*. (117) have also shown that the NTS cells mediate nicotine-stimulated NE release in the amygdala and hippocampus through nAChRs. Finally, nicotine has been shown to act on CA neurons in the NTS, area postrema, and rostral ventro-lateral medulla altering centrally-mediated cardiovascular responses (118).

6. NICOTINIC REGULATION OF CATECHOLAMINES IN THE DEVELOPING BRAIN

6.1. Developmental Appearance of Catecholamine Neurons: Introduction

Considerable literature (32,119) indicates that nAChRs in skeletal muscle and peripheral ganglia are developmentally regulated. The pharmacological characteristics of nAChRs in these systems change with age, suggesting a dynamic modulation throughout development. There have been few studies which have examined the functional properties of nAChRs in the developing brain (120). However, a number of studies have demonstrated developmental changes in CNS mRNA (121-123) and protein expression (104,124,125).

[^{3}H]Nicotine binding sites are abundant in regions of developing CA nerve cells, in that there is a high density of overlap of CA cells and nicotinic binding sites in areas such as the substantia nigra (9). Ascending and descending CA projections are continually forming from gestational day 15 through the early postnatal period (9,126). Thus, depending upon when nicotine is administered the effect on the developing neuronal circuitry will differ. For instance, there is early innervation of many brain regions by terminals of the LC (127), and developing NE neurons are particularly sensitive to prenatal nicotine exposure (128). This sensitivity is critical because NE has been shown to significantly influence cellular development (129).

6.2. Developmental Appearance of Dopamine Neurons

Nicotine binding sites have been identified on both the cell bodies and terminals of dopaminergic neurons (130). The detection of prenatal dopaminergic cell groups is ubiquitous. Morphological and/or biochemical techniques have been used to detect DA as early as day 12 of gestation in rats (131-135), day 13 in mice (134), day 14 in rabbits (135) and 5.5 weeks in humans (136). Hence, there is evidence for very early appearance, migration, differentiation, and functional development of dopaminergic neurons across many species. Furthermore, DA levels increase throughout development (132,136). Nicotinic receptors are densely distributed through the SNC and VTA and at least one-third of striatal nicotine binding sites are located on dopamine terminals (57).

6.3. Developmental Appearance of Noradrenergic Neurons

Pontine NE cells are born between E10 and E13 (137) and first exhibit tyrosine hydroxylase (TH) immunoreactivity on E12 in the rat (138,139). In humans, TH and dopamine-β-hydroxylase immunoreactivities are present in a region corresponding to the anlage of the LC and associated NE nuclei by the sixth week of gestation (140,141). This translates roughly to an equivalent point in rat development (142). A well-organized CA system in embryonic stages could be important for normal shaping of the nervous system (140).

Detection of nAChRs closely follows the early appearance of NE cells. While nicotinic cholinergic binding sites have been detected in pontine regions as early as E13-E14 in rat (104) it cannot be concluded that these localize to NE cells. However, *in situ* hybridization studies have revealed developmental expression of various nAChR subunit mRNAs in the LC with appearances at E17 using oligonucleotide probes (122) or E15 using the more sensitive riboprobes (38). We have found that LC cells express a number of nicotinic subunits during development and in the adult (38). Some of these appear to be developmentally regulated. This is significant because not

only does it suggest the possibility of several distinct nAChRs, it also allows for functional differences depending on the stage of maturation.

The presence of nicotinic binding sites or their mRNAs in embryogenesis does not affirm protein functionality. It is possible that the necessary signal transduction machinery downstream of the receptor is not yet in place, or in the case of the nAChR, the ion channel may not yet regulate the flow of ions. One interpretation of chronic prenatal exposure to nicotine is that the upregulation of nicotinic binding sites is evidence for cellular adaptation to nicotine, and hence a functional response (143). Using a dissociated tissue culture model, we have shown that LC cells taken from E14 embryos respond to nicotine stimulation after four days *in vitro* (120).

6.4. Confounds in Developmental Experiments

Administering nicotine to the pregnant dam has many confounds. Treating the animal with daily nicotine injections would require either many small doses or few comparatively high doses. Frequent injections could cause handling stress, while high doses lead to elevated plasma nicotine peaks, prone to cause fetal hypoxia (144). As an alternative to injections, nicotine has been administered in the drinking water. However, this could be problematic because the animals fluid intake could decrease to undesirable levels (144). To circumvent these problems osmotic minipumps are often implanted to obtain doses similar to human smokers. Moreover, significant route-related changes in brain DA and NE and their metabolites have been reported (145). One of the most vulnerable periods in brain development for nicotine exposure in rodents appears to be during the second postnatal week (146,147) which roughly corresponds to the last trimester of human gestation (142).

6.5. Prenatal Nicotine Exposure on Development of Dopamine Neurons

Nicotine can exert acute effects on central fetal dopamine systems. Acute injection of nicotine to pregnant dams at gestational day (GD) 21 causes DA and its metabolites 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) to increase in the forebrain of male and female rat fetuses (148). Therefore, acute nicotine treatment stimulates DA release in the fetal rat brain. As compared to the response of adult rats acutely injected with the same dose, nicotine causes increased firing of nigral DA neurons, DA turnover and striatal HVA, but no change in DOPAC (149). Although the research is limited, the data emphasizes an acute responsiveness of fetal dopaminergic systems to nicotine.

Chronic prenatal exposure to nicotine results in long-lasting changes in DA systems. Chronic nicotine administration to the pregnant dam via minipump causes an increase in forebrain DOPAC in GD18 male fetuses. This is in contrast to both chronically exposed GD18 females whose DOPAC was at control levels and acutely exposed GD21 females whose DOPAC was significantly increased. By two weeks of age (prenatal day 15; PN15) the DOPAC levels are further increased in the forebrain of male offspring and there is a rise in forebrain DA in both sexes (148). At adulthood (2.5 months), males have reduced levels of forebrain DOPAC and HVA, and females have reduced levels of forebrain HVA (148). Forebrain DA turnover was reduced in males at PN15 (145,148) and in both sexes at adulthood (148). Also, it has been reported that tyrosine hydroxylase activity was reduced in the caudate-putamen of juvenile, PN20 and PN40, rats prenatally exposed to nicotine (150). In another study, PN14 rats showed no significant change in the levels of striatal DA or DOPAC, yet, there was a reduction in the number of striatal DA receptor binding sites as well as an increase in the affinity of these receptors in the male nicotine-exposed pups (151). It was also reported that there was no significant change in the number of nicotinic receptor binding sites in the striatum of the PN14-prenatally exposed pups (151). In contrast, chronic nicotine administration to the pregnant dam caused increased nicotinic receptor binding sites in fetal brains (152) and in the midbrain + brainstem and cerebral cortex of PN14 nicotine-exposed offspring (128). Thus, the effect of nicotine on the developing brain may exhibit regional and sexual differences.

One of the most prominent signs of basal ganglia (including the striatum) disorders is motor disturbances. Fung *et al*. (153) demonstrated that PN14 prenatally nicotine-exposed male and female rats were spontaneously hyperactive. However, Schlumpf *et al*.(154) found that prenatally exposed PN7 males were initially hypoactive and became hyperactive at PN15, while female pups were not influenced by prenatal nicotine. Similarly, Shacka *et al*. (155) suggested that central control of motor function may be more vulnerable to prenatal nicotine in males since prenatally treated PN14 males, not females displayed profound hyperlocomotion following a nicotine challenge. In early adulthood, mouse pups prenatally exposed to nicotine were hyperactive, indicating a long-lasting effect (156). Hence, prenatal nicotine exposure may be altering the normal development of striatal dopaminergic neurons.

6.6. Prenatal Nicotine Exposure on Development of Noradrenergic Neurons

In the developing brain there is early innervation of many brain regions by terminals of the LC (127,157), and NE has been shown to significantly influence cellular development (129). Therefore, developing NE neurons are particularly sensitive to prenatal nicotine exposure (128). Behavioral tests designed to elicit cognitive deficits have revealed various limitations in animals exposed to nicotine *in utero* (158) which persist in adulthood. There is, however, considerable question as to whether the observed effects are direct or indirect (159). Although intermittent peripheral administration of nicotine to the dam significantly increases NE neuronal activity (128), different effects are observed after chronic infusion (128,148). It has therefore been proposed that the stimulant effects of nicotine are induced by hypoxia (128). The indirect action is suggested by studies which failed to detect acute nicotine-induced stimulation of NE turnover during the perinatal period (48,159). However, continuous prenatal

nicotine exposure ablates the ability of a subsequent postnatal nicotine challenge to release NE (27). Furthermore, animals exposed to nicotine by chronic infusion during late gestation exhibit an aberrant central release of NE in response to neonatal hypoxia (160). Slotkin and colleagues have suggested that this neurochemical response may be significant in mediating respiratory adjustments, and that this may represent a defect seen in infants with SIDS. Alternate mechanisms have also been proposed (161,162).

Anatomical studies have examined nAChR expression using binding studies. The results of these experiments appear somewhat equivocal until numerous variables are elaborated. Prenatal nicotine insult results in a transient increase in overall numbers of nAChRs, which appear to normalize by the sixth postnatal week in rats (128,163). Some studies have not examined measurements beyond the first month of life (164,165) leading to a premature assumption of persistent overall elevation in receptor number. However, selective regional measurement of brains exposed postnatally to nicotine reveals permanent alterations in nAChRs in cortex, hippocampus and striatum (147).

7. POSTNATAL OBSERVATIONS FOLLOWING PRENATAL NICOTINE

Although numerous animal studies have provided evidence that perinatal nicotine exposure significantly alters developmental outcome, the exact effects are extremely dependent on dose, age and route of administration. However, there have been consistent observations of long-term changes in neuroendocrine status (166-168), cognitive function (158,169-171), and locomotor activity (153,154,156,172), following pre- or post-natal chronic nicotine treatment. It has recently been shown that pups born of rats exposed to sidestream smoke had a dose-dependent reduction of birth weight and a dose-independent ossification retardation (173). In addition, both acute and chronic nicotine administration have been shown to induce altered responses to hypoxia in the neonate (160,162,174). Perinatal exposure to nicotine has been shown to impair the ability of rat pups to autoresuscitate from repeated exposure to hypoxia (175). Further, prenatally exposed pups had chronic hypoventilation (176). These effects may play a role in sudden infant death syndrome. Although some changes may be mediated indirectly via uteroplacental constriction and metabolic effects (177), it has been shown that nicotine can also significantly impact neurobehavioral development when administered by chronic infusion at doses that do not alter fetal growth (128). Such findings suggest that central nicotinic receptors (nAChRs) are functional early and may serve an important role in modulating neuronal development.

7.1. Post-Natal Effects: Gender Differences

Accumulating evidence indicates that numerous responses to prenatal nicotine exposure are sex-related (155,158,164,178). While locomotor activity has already been addressed, another behavioral measure is the prepulse inhibition (PPI) of the acoustic startle response. This test measures changes in time-dependent sensory-motor gating. Deficits in this gating are thought to underlie part of the decreased vigilance and attention observed in children of mothers who smoked cigarettes during pregnancy. Popke *et al*. (163) found that prenatal nicotine exposure alters prepulse inhibition in adolescent female rats, without any obvious changes in nAChR binding. A 10 year study found that children whose mothers smoked at least 10 cigarettes a day during pregnancy had a 4-fold increased risk of prepubertal-onset conduct disorder in boys and a 5-fold increased risk of adolescent-onset drug dependence in girls as compared to children whose mothers did not smoke (179). One conceivable explanation for gender-differences involves the difference in hormonal milieu between males and females during development. However, the mechanism(s) behind these differences are at present only speculation.

8. CONCLUSION

The influence of nicotine on the development of central NA and DA pathways is of particular interest, given their putative trophic role in CNS ontogeny (129). Thus, it has been suggested that some of the prominent effects of prenatal nicotine exposure may result from disruption of the development of these systems (9). Precisely how prenatal exposure to nicotine causes postnatal neurobehavioral disturbances and growth retardation is not known. Early studies proposed that nicotine exerts its disruptive influence in the CNS indirectly through its action at peripheral nAChRs, leading to episodic hypoxia and ischemia (180-183). More recent evidence suggests that this alkaloid also acts directly at central nicotinic receptors and is involved in modulation of neurotransmitter release (52,111,120,184,185), often by acting on nAChRs located pre-synaptically. Early expression of nAChR mRNA and protein in developing mammalian CNS allows for the possible direct action of nicotine (104,122,125,186). However, various *in vivo* studies suggest that nicotine's effect on NE in the developing brain are indirect (183,187).

In order to understand how nicotine exerts its effect, scientists can examine affected systems for morphological, biochemical, and functional changes resulting from nicotine exposure. Most studies which examine nicotine stimulated release of neurotransmitters have been carried out using adult brain, and there is very little published data on the effects in developing brain. Extrapolation of data from mature nervous tissue to the developing system is not wise since nicotine appears to affect the overall development of a number of systems, and may affect brain tissue differently. For example, acute nicotine administration causes release of NE and DA in the adult nervous system, yet fetal exposure to nicotine leads to deficiencies in these same systems when assessed postnatally (27). What is becoming increasingly clear, is that nicotine causes premature differentiation of developing neural tissue (187) and elicits functional alterations in noradrenergic and dopaminergic pathways in the central nervous system (27,182).

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