Cellular and Molecular Neurobiology, Vol. 8, No. 3, 1988

Commentary

Hypothesis: A Nicotine–Dopamine Interaction Linking Smoking with Parkinson's Disease and Tardive Dyskinesia

Darrell G. Kirch,[1,2] Anna-Maria Alho,[1] and Richard Jed Wyatt[1]

Accepted February 18, 1988

KEY WORDS: nicotine; dopamine; smoking; Parkinson's disease; tardive dyskinesia.

SUMMARY

1. Nicotine, an important pharmacological component of cigarette smoke, is known to have significant effects on central nervous system (CNS) dopaminergic function. Although acute doses of nicotine have been shown to facilitate dopamine release, recent data indicate that chronic nicotine treatment may actually decrease CNS dopamine turnover in the striatum.

2. A number of epidemiological investigations have demonstrated that individuals who are or who have been smokers are *less* likely to develop idiopathic Parkinson's disease (a disorder involving a deficit in nigrostriatal dopaminergic neurotransmission). In addition, there is preliminary evidence that individuals with tardive dyskinesia (a hyperkinetic movement disorder observed in some cases of chronic neuroleptic treatment and thought by some to be associated with striatal dopamine receptor supersensitivity) are *more* likely to be smokers.

3. A unitary hypothesis is presented, proposing that smoking in early adult life may decrease CNS catecholamine turnover, thereby protecting against free radical formation from catecholamine oxidation that in turn damages striatal neurons. These individuals are thereby "protected" from the later development of Parkinson's disease. In this hypothetical scheme, individuals who are given

[1] Neuropsychiatry Branch, National Institute of Mental Health, William A. White Building, Washington, D.C. 20032.
[2] To whom correspondence should be addressed.

0272-4340/88/0900-0285$06.00/0

neuroleptics and who also are smokers may develop a greater degree of dopamine receptor supersensitivity due to combined receptor blockade by neuroleptics and a decrease in CNS dopamine turnover caused by nicotine, resulting in an increased prevalence of tardive dyskinesia in this group.

INTRODUCTION

Much basic and clinical research has been devoted to studying the complex neuroregulatory effects of cigarette smoking (Pomerleau and Pomerleau, 1984; Benowitz, 1986), and it is generally accepted that the key pharmacologically active agent involved in these effects is nicotine (Clarke, 1987). Nevertheless, much remains unknown regarding the effects of nicotine on central nervous system (CNS) function at the cellular and molecular level. This commentary represents an attempt to combine intriguing epidemiological observations regarding two neurological movement disorders that involve dopaminergic dysfunction, Parkinson's disease and tardive dyskinesia, with basic research findings regarding the effects of nicotine on CNS dopamine. The result is a hypothesis regarding a pathophysiological role for nicotine in protecting against Parkinson's disease and in predisposing toward tardive dyskinesia.

SMOKING AND PARKINSON'S DISEASE

The etiology of Parkinson's disease remains unknown and may involve genetic factors, environmental agents, and/or even the normal aging process (Calne and Langston, 1983). In some cases, such as the toxic, post-encephalitic, or familial forms of the disorder, there are clues to the cause. The vast majority of cases, however, is idiopathic. The neuropathology of the disorder involves loss of dopaminergic neurons located in the substantia nigra, resulting in a nigrostriatal dopaminergic deficit and the clinical picture of bradykinesia, rigidity, tremor, and loss of postural reflexes.

Although the detrimental medical effects of smoking are well documented (Benowitz, 1986), a number of investigators have concluded that individuals with Parkinson's disease are less likely to currently be or in the past to have been cigarette smokers. These studies have been recently reviewed by Baron (1986). The initial epidemiological evidence regarding a negative association between smoking and Parkinson's disease came from analysis by Kahn (1966) of data from the large-scale Dorn study of smoking and mortality in veterans. A lower mortality ratio for Parkinson's disease was noted, not only for current cigarette smokers but also for ex-cigarette smokers. An extensive study of mortality among British physicians noted a similar trend (Doll and Peto, 1976). In addition to mortality reviews, a number of investigators have assessed smoking behavior in groups of patients with Parkinson's disease and matched controls. The majority of these studies has confirmed the negative association between smoking and Parkinson's disease, most reporting a relative risk of approximately 0.5, with

smokers half as likely to develop Parkinson's disease as nonsmokers (Baron, 1986). In some studies there even appears to be a "dose–response" relationship between the quantity of smoking and the risk of Parkinson's disease (Godwin-Austen *et al.*, 1982; Baron, 1986). Perhaps most convincing are those studies that analyzed data from twin pairs. There is a low concordance among monozygotic twin pairs for Parkinson's disease, suggesting a relatively minor role for genetic factors in the etiology of this disorder (Ward *et al.*, 1983). In a recent study examining a number of environmental factors in 31 monozygotic twin pairs discordant for Parkinson's disease, Bharucha and colleagues (1986) found that the only statistically significant difference was that the affected twins were less likely to be or to have been cigarette smokers, even at age 30, years before the apparent onset of Parkinson's disease.

It should be noted that not all investigators have concluded that smoking confers a protective effect in relation to Parkinson's disease (Golbe *et al.*, 1986; Rajput *et al.*, 1987). Nevertheless, these negative findings are in the minority. Obviously, even if this lower relative risk is valid, it does not confirm a causal link. There may be some third factor involved. Some investigators have suggested a possible difference in premorbid personality between those who develop Parkinson's disease and those who do not (Todes and Lees, 1985), with the former having a personality style (perhaps related to the underlying pathophysiology that ultimately causes their disease) that makes them less likely to smoke.

SMOKING AND TARDIVE DYSKINESIA

In contrast to the bradykinesia of Parkinson's disease, tardive dyskinesia is a hyperkinetic movement disorder characterized by choreoathetoid movements, observed in a significant number of patients chronically treated with neuroleptics (Jeste and Wyatt, 1982). A leading hypothesis regarding the etiology of tardive dyskinesia is that dopamine receptor blockade by neuroleptics induces development of striatal receptor supersensitivity that is pathophysiologically responsible for the dyskinetic movements, although other mechanisms have also been considered (Jeste and Wyatt, 1981).

Much less attention has been paid to the epidemiology of smoking in relation to tardive dyskinesia. There are indications, however, that smokers are more likely than nonsmokers to have tardive dyskinesia. Two groups (Yassa *et al.*, 1987; Binder *et al.*, 1987) have noted this association in surveys of chronic psychiatric patients. Our own data (submitted for publication) from a survey of inpatient admissions not only show that patients with tardive dyskinesia are more likely to be smokers, but also indicate that smokers with tardive dyskinesia may have higher blood levels of nicotine and its metabolite, cotinine, than smokers without tardive dyskinesia. It is unlikely that smoking is simply linked to tardive dyskinesia via a pharmacokinetic interaction with neuroleptic medications resulting in increased neuroleptic concentrations, since initial studies have indicated that smoking tends actually to decrease plasma neuroleptic levels (Jann *et al.*, 1986). These data showing a positive association between smoking and tardive

dyskinesia must be viewed as preliminary, at best, and await larger-scale confirmatory studies of the type reported above for Parkinson's disease.

NICOTINE AND DOPAMINE

The apparent contrasting negative association between smoking and Parkinson's disease and positive association between smoking and tardive dyskinesia, together with the fact that both disorders appear to be pathophysiologically linked to striatal dopaminergic dysfunction, raise the question of interactions between nicotine and dopamine in the CNS. The neuropharmacology of nicotine is complex and may involve multiple neurotransmitter systems (Balfour, 1982). Nicotine appears to bind to multiple types of receptors both centrally and peripherally and may directly affect noncholinergic neurons. For example, there appears to be binding of nicotine at receptors on nigrostriatal and mesolimbic dopaminergic neurons (Clarke and Pert, 1985).

A number of studies have explored the effects of nicotine on CNS dopaminergic function. These have used both *in vitro* and *in vivo* paradigms. Some investigators have noted nicotine-induced dopamine release from rat brain striatal, hypothalamic, and hippocampal slices (Goodman, 1974; Arqueros *et al.*, 1978; Giorguieff-Chesselet *et al.*, 1979). Similarly, nicotine-induced dopamine release from synaptosomal preparations (Connelly and Littleton, 1983) and from neuron-enriched tissue cultures (Barochovsky and Bradford, 1987) has been reported. Firing of neurons in the substantia nigra zona compacta in anesthetized rats was stimulated by nicotine administered iontophoretically (Lichtensteiger *et al.*, 1982) and systemically (Clarke *et al.*, 1985). It is important to note, however, that most of the *in vivo* studies used either a single acute injection of nicotine or a brief series of injections, and the *in vitro* studies used tissue perfusion (Kirch *et al.*, 1987).

In an attempt to parallel more closely the pattern of nicotine self-administration observed in humans, we chronically infused rats with nicotine (3 or 12 mg/kg/day) subcutaneously using osmotic minipumps (Kirch *et al.*, 1987). After 21 days of treatment, high-performance liquid chromatographic analysis of brain tissue showed a significant decrease in dopamine turnover in the striatum, hypothalamus, and frontal cortex in nicotine-treated versus control animals, a marked contrast to the increase in dopamine release observed with acute doses of nicotine. The apparent opposite effect of acute doses of nicotine versus chronic treatment may in part explain the development of tolerance to many of the acute effects of nicotine in regular smokers.

Nicotine also affects CNS norepinephrine, serotonin, and a number of peptides (Balfour, 1982; Kirch *et al.*, 1987). For example, acute doses of nicotine have been reported to increase norepinephrine release (Goodman, 1974; Arqueros *et al.*, 1978). The changes in other monoamines and peptides are complex and (as in the case of dopamine) vary with the experimental design, in particular the dosing strategy. It remains unclear whether any design for nicotine administration, even pump infusions for several weeks, is adequate as a model for the kind of chronic exposure to nicotine that humans experience.

A HYPOTHETICAL CONNECTION AMONG NICOTINE, PARKINSON'S DISEASE, AND TARDIVE DYSKINESIA

In examining the apparent protective effect of smoking in relation to Parkinson's disease, other investigators have focused on the ability of nicotine to stimulate CNS dopamine release (Baron, 1986). In this view, the protective effect of smoking in Parkinson's disease could be due to increased dopamine release from remaining neurons, and the link between smoking and tardive dyskinesia would be due to nicotine-induced dopamine release onto receptors made supersensitive by neuroleptic treatment (Yassa *et al.*, 1987). This theory, however, is inconsistent with the decrease in striatal dopamine turnover indicated by our own data (Kirch *et al.*, 1987).

If smoking is negatively associated with Parkinson's disease and positively associated with tardive dyskinesia (as epidemiological studies indicate), and if the effect of chronic nicotine is to decrease striatal dopamine turnover, then the following hypothesis must be considered. Perhaps as one smokes through early and middle adult life, a nicotine-induced decrease in striatal dopamine turnover actually decreases the amount of catecholamines that are oxidized to form free radicals, agents that in turn may damage dopaminergic neurons (Graham *et al.*, 1978; Cohen, 1984). The smoker is thereby protected against the loss of nigrostriatal dopaminergic neurons that in later adult life, if severe enough, would be manifested as Parkinson's disease. On the other hand, the patient with neuropsychiatric illness who is being treated chronically with neuroleptics and who is also a smoker may be more prone to develop dopamine receptor supersensitivity as the cumulative result of both postsynaptic receptor blockade by neuroleptics and a nicotine-induced decrease in dopamine turnover.

Clearly, certain aspects of this hypothesis are open to criticism. The proposal that neuronal toxicity caused by the oxidative formation of free radicals from catecholamines is involved in the etiology of Parkinson's disease is controversial (Perry *et al.*, 1982; Cohen, 1984). Nevertheless, evidence for a similar process is seen in the model of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) toxicity, which appears to cause a parkinsonian syndrome via the production of free radicals (Langston, 1985). Even if free radical formation does prove to be a factor in Parkinson's disease, another possible explanation of the apparent protective effect of smoking might be that it helps prevent free radical formation by creating a more reducing environment due to higher concentrations of carbon monoxide (Calne and Langston, 1983).

Another area of debate is the actual mechanism whereby neuroleptic treatment is associated with tardive dyskinesia. Although the concept of neuroleptic-induced postsynaptic dopamine receptor supersensitivity has been accepted as "dogma," other mechanisms such as increased presynaptic dopamine release or noradrenergic hyperactivity may be pathophysiologically relevant (Jeste and Wyatt, 1981). Nicotine also clearly affects CNS noradrenergic systems (Arqueros *et al.*, 1978; Kirch *et al.*, 1987).

Although the hypothesis we have presented admittedly is speculative, it represents an initial attempt at a parsimonious integration of the available epidemiological facts, major theories concerning the neuropathophysiology of

Parkinson's disease and tardive dyskinesia, and basic science data on nicotine–dopamine interactions. This hypothesis is presented solely to aid in focusing further basic and clinical investigation. One key aspect of the hypothesis in need of expanded study is the chronic effect of nicotine on pre- and postsynaptic dopaminergic function, as well as on other monoamines. Insofar as humans appear to smoke in a fashion that maintains significant nicotine concentrations through the day (Benowitz, 1986), the use of *in vivo* experimental designs involving chronic nicotine infusions would seem to be optimal. Work is currently in progress in our laboratory to determine whether chronic nicotine treatment does alter dopamine receptor numbers or affinity and to assess nicotine–neuroleptic interactions and effects on CNS monoamines. As these effects are better understood, we will still face the problem of extrapolating from these results in animals to the CNS of patients with psychosis. These patients may very well have underlying CNS neurotransmitter abnormalities that are present long before exposure to any drug. The lack of an adequate animal model of psychosis is a basic neuroscientific problem that will make it especially difficult to elucidate fully the effects of nicotine in humans with and without psychosis.

REFERENCES

Arqueros, L., Naquira, D., and Zunino, E. (1978). Nicotine-induced release of catecholamines from rat hippocampus and striatum. *Biochem. Pharmacol.* **27:**2667–2674.

Balfour, D. J. K. (1982). The effects of nicotine on brain neurotransmitter systems. *Pharmacol. Ther.* **16:**269–282.

Barochovsky, O., and Bradford, H. F. (1987). Modulation of dopamine release from neuron-enriched tissue cultures by cholinergic agents. *J. Neurochem.* **48:**798–803.

Baron, J. A. (1986). Cigarette smoking and Parkinson's disease. *Neurology* **36:**1490–1496.

Benowitz, N. L. (1986). Clinical pharmacology of nicotine. *Annu. Rev. Med.* **37,** 21–32.

Bharucha, N. E., Stokes, L., Schoenberg, B. S., Ward, C., Ince, S., Nutt, J. G., Eldridge, R., Calne, D. B., Mantel, N., and Duvoisin, R. (1986). A case-control study of twin pairs discordant for Parkinson's disease: A search for environmental risk factors. *Neurology* **36:**284–288.

Binder, R. L., Kazamatsuri, H., Nishimura, T., and McNeil, D. E. (1987). Smoking and tardive dyskinesia. *Biol. Psychiat.* **22:** 1280–1282.

Calne, D. B., and Langston, J. W. (1983). Aetiology of Parkinson's disease. *Lancet* **2:**1457–1459.

Clarke, P. B. S. (1987). Nicotine and smoking: A perspective from animal studies. *Psychopharmacology* **92:**135–143.

Clarke, P. B. S., and Pert, A. (1985). Autoradiographic evidence for nicotine receptors on nigrostriatal and mesolimbic dopaminergic neurons. *Brain Res.* **348:**355–358.

Clarke, P. B. S., Hommer, D. W., Pert, A., and Skirboll, L. R. (1985). Electrophysiological actions of nicotine on substantia nigra single units. *Br. J. Pharmacol.* **85:** 827–835.

Cohen, G. (1984). Oxy-radical toxicity in catecholamine neurons. *Neurotoxicology* **5:**77–82.

Connelly, M. S., and Littleton, J. M. (1983). Lack of stereoselectivity in ability of nicotine to release dopamine from rat synaptosomal preparations. *J. Neurochem.* **41:**1297–1302.

Doll, R., and Peto, R. (1976). Mortality in relation to smoking: 20 years' observations on male British doctors. *Br. Med. J.* **2:**1525–1536.

Giorguieff-Chesselet, M. F., Kemel, M. L., Wandscheer, D., and Glowinski, J. (1979). Regulation of dopamine release by presynaptic nicotinic receptors in rat striatal slices: Effect of nicotine in a low concentration. *Life Sci.* **25:**1257–1262.

Godwin-Austen, R. B., Lee, P. N., Marmot, M. G., and Stern, G. M. (1982). Smoking and Parkinson's disease. *J. Neurol. Neurosurg. Psychiat.* **45:**577–581.

Golbe, L. I., Cody, R. A., and Duvoisin, R. C. (1986). Smoking and Parkinson's disease: Search for a dose-response relationship. *Arch. Neurol.* **43:**774–778.

Goodman, F. R. (1974). Effects of nicotine on distribution and release of ^{14}C-norepinephrine and ^{14}C-dopamine in rat brain striatum and hypothalamus slices. *Neuropharmacology* **13:**1025–1032.

Graham, D. G., Tiffany, S. M., Bell, W. R., and Gutknecht, W. F. (1978). Autoxidation versus covalent binding of quinones as the mechanism of toxicity of dopamine, 6-hydroxydopamine, and related compounds toward C1300 neuroblastoma cells *in vitro*. *Mol. Pharmacol.* **14:**644–653.

Jann, M. W., Saklad, S. R., Ereshefsky, L., Richards, A. L., Harrington, C. A., and Davis, C. M. (1986). Effects of smoking on haloperidol and reduced haloperidol plasma concentrations and haloperidol clearance. *Psychopharmacology* **90:**468–470.

Jeste, D. V., and Wyatt, R. J. (1981). Dogma disputed: Is tardive dyskinesia due to postsynaptic dopamine receptor supersensitivty? *J. Clin. Psychiat.* **42:**455–457.

Jeste, D. V., and Wyatt, R. J. (1982). *Understanding and Treating Tardive Dyskinesia,* Guilford Press, New York.

Kahn, H. A. (1966). The Dorn study of smoking and mortality among U.S. veterans: Report on eight and one-half years of observation. In *Epidemiological Approaches to the Study of Cancer and Other Chronic Diseases* (W. Haenszel, Ed.), U.S. Department of Health, Education and Welfare, National Cancer Institute Monograph 19, pp. 1–27.

Kirch, D. G., Gerhardt, G. A., Shelton, R. C., Freedman, R., and Wyatt, R. J. (1987). Effect of chronic nicotine administration on monoamine and monoamine metabolite concentrations in rat brain. *Clin. Neuropharmacol.* **10:**376–383.

Langston, J. W. (1985). MPTP and Parkinson's disease. *TINS* **8:**79–83.

Lichtensteiger, W., Hefti, F., Felix, D., Huwyler, T., Melamed, E., and Schlumpf, M. (1982). Stimulation of nigrostriatal dopamine neurones by nicotine. *Neuropharmacology* **21:**963–968.

Perry, T. L., Godin, D. V., and Hansen, S. (1982). Parkinson's disease: A disorder due to nigral glutathione deficiency? *Neurosci. Lett.* **33:**305–310.

Pomerleau, O. F., and Pomerleau, C. S. (1984). Neuroregulators and the reinforcement of smoking: Towards a biobehavioral explanation. *Neurosci. Biobehav. Rev.* **8:**503–513.

Rajput, A. H., Offord, K. P., Beard, C. M., and Kurland, L. T. (1987). A case-control study of smoking habits, dementia, and other illnesses in idiopathic Parkinson's disease. *Neurology* **37:**226–232.

Todes, C. J., and Lees, A. J. (1985). The pre-morbid personality of patients with Parkinson's disease. *J. Neurol. Neurosurg. Psychiat.* **48:**97–100.

Ward, C. D., Duvoisin, R. C., Ince, S. E., Nutt, J. D., Eldridge, R., and Calne, D. B. (1983). Parkinson's disease in 65 pairs of twins and in a set of quadruplets. *Neurology* **33:**815–824.

Yassa, R., Lal, S., Korpassy, A., and Ally, J. (1987). Nicotine exposure and tardive dyskinesia. *Biol. Psychiat.* **22:**67–72.