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Tobacco, coffee, and Parkinson’s disease

Caffeine and nicotine may improve the health of dopaminergic systems

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arkinson’s disease belongs to that small group of conditions that occur less often among cigarette smokers than in non-smokers. The observation was first made in a case-control study over 30 years ago, but, as Hernán and colleagues have shown in their recent systematic review and meta-analysis, the finding has been replicated many times. The protective effect is large—according to the pooled data, current smokers have a 60% reduction in risk compared with those who have never smoked—and consistent between studies in different settings. The fact that two very large prospective studies found a similar reduction in risk to that seen in retrospective studies rules out the possibility that the association can be accounted for by differential survival between smokers and non-smokers. Coffee drinking too, seems to protect against Parkinson’s disease. Here the pooled estimate is a 30% reduction in risk for coffee drinkers compared with non-drinkers.

In “An Essay on the Shaking Palsy,” James Parkinson noted that his first case “had industriously followed the business of a gardener, leading a life of remarkable temperance and sobriety.” Since then several small studies have implied that people with Parkinson’s disease tend to exhibit traits such as inflexibility, caution, and lack of novelty seeking even before they have developed motor symptoms. This idea has never been tested in a large prospective study, but it does raise the possibility that people who will later develop Parkinson’s disease are constitutionally less likely to feel the need for the type of stimulation provided by tobacco and coffee. This might occur if the genetic determinants of likelihood and intensity of behaviours such as cigarette smoking and coffee drinking were the same or closely linked to the genes that determined susceptibility to Parkinson’s disease. If so, any apparent protective effect might be the result of confounding. The authors of the systematic review explored this possibility in a sensitivity analysis. They made the fairly extreme assumption that such a genetic combination was present in a third of the population and conferred both a fivefold increase in risk of Parkinson’s disease and, simultaneously, a fivefold decrease in likelihood of taking up smoking. Even after adjusting for a genetic influence of this strength, smoking still conferred more than a 50% reduction in risk.

If confounding by a genetic haplotype looks unlikely, what other reasons remain? A theoretical possibility is that the relation between cigarette smoking or coffee drinking and Parkinson’s disease is operating in the reverse direction. In other words, Parkinson’s disease makes people less likely to smoke or drink coffee. Of course these habits are usually acquired by early adult life, whereas symptoms of Parkinson’s disease are rare before late middle age. So this explanation could be correct only if the subclinical phase of the disease is very much longer than we currently believe.

Perhaps it is more plausible that substances present in coffee and tobacco—caffeine and nicotine are obvious candidates—have a central action that improves the health of dopaminergic systems. Evidence in support of caffeine’s role as a neuroprotectant has recently emerged from a study using a mouse model of Parkinson’s disease. Mice that were pretreated with caffeine before exposure to the dopaminergic neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) lost less striatal dopamine and fewer dopamine transporter binding sites. Caffeine’s apparent neuroprotective effect may be due to its ability to block adenosine A2A receptors that are concentrated in the dopamine rich areas of the brain. Adenosine decreases dopaminergic neurotransmission by means of antagonistic interactions between A2A receptors and dopamine receptors. The blockade of these receptors can therefore facilitate dopaminergic transmission by stimulating dopamine release and by potentiating the effects of dopamine receptor stimulation. Knockout mice that lack functional adenosine A2A receptors are also resistant to the dopamine depleting effects of MPTP. Like caffeine, nicotine has been found to reduce MPTP-induced dopaminergic toxicity in animal models of Parkinson’s disease. One mechanism under-
lying this protective action may be its ability to increase the expression of neurotrophic factors that are known to promote survival of dopaminergic neurons.1 But tobacco contains numerous other chemicals whose influence on biological processes may play a part. Smoking causes a reduction in activity of monoamine oxidase A and B, for example, which might protect against neuronal damage by inhibiting the enzymatic oxidation of dopamine.1

One unachieved goal in the treatment of Parkinson’s disease is preventing it getting worse. If, as the epidemiological evidence implies, caffeine and nicotine are neuroprotective, some of the new pharmacological treatments currently being developed, such as adenosine A<sub>2A</sub> receptor blockers and nicotinic agonists, might not only improve symptoms but slow the relentless progression of the disease.

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