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Review

Methamphetamine use and future risk for Parkinson's disease: Evidence and clinical implications

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ABSTRACT

Background: Methamphetamine use has been posited to be a risk factor for the development of Parkinson's disease (PD) and parkinsonism. The clinical implications of a potential association between methamphetamine use and PD are considered.

Methods: A review of methamphetamine and PD and parkinsonism was conducted, including evidence from animal models, clinical and population studies.

Results: There is biological plausibility to a link between methamphetamine use and PD. Though clinical and epidemiological evidence in this area is scant, a number of studies suggest that methamphetamine is associated with a moderately increased risk of PD and parkinsonism, and may also lead to premature onset of PD. The long lag time between exposure to methamphetamine and onset of PD, the potential for recovery from neurotoxic effects, and tobacco smoking each may attenuate the association. Individual and drug use characteristics that may modulate a user's risk remain poorly understood.

Conclusions: The use of methamphetamine may be an initiating event in the development of PD and parkinsonism, in addition to other risk factors that a given individual may hold. Clinicians should be vigilant to signs of prodromal and emerging PD among methamphetamine users. In individuals with premature onset illness, information on current or prior exposure to methamphetamine should be sought.

1. Introduction

Methamphetamine use is a significant public health problem, with an estimated 35 million stimulant users worldwide, predominantly of methamphetamine (Degenhardt and Hall, 2012; Degenhardt et al., 2013; UNODC, 2016). Harmful physical and mental health consequences are common, including cardiovascular and cerebrovascular pathology, psychosis, suicide and premature mortality (Callaghan et al., 2012a; Darke et al., 2008, 2011; Karch, 2015). The stimulants methamphetamine and its active metabolite amphetamine are highly related and are hereafter referred to as methamphetamine (McKetin et al., 2016)

There has been recent speculation that methamphetamine use may be associated with greater risk of developing Parkinson's disease (PD). Here, we examine the question whether methamphetamine users are at increased risk of PD or parkinsonism. There is an extensive pre-clinical literature investigating the effects of methamphetamine on brain tissue, and specifically its propensity to cause brain dopamine neuronal damage such as that observed in Parkinson's disease. This literature has been comprehensively reviewed elsewhere (Kish et al., 2017). The current review extends beyond these preclinical findings by reviewing evidence from clinical and population studies of PD and parkinsonism among individuals exposed to methamphetamine. The clinical implications for methamphetamine users, their communities and clinicians are considered.

1.1. Pathology of Parkinson's disease and parkinsonism

PD is characterized by the clinical manifestations of bradykinesia in combination with rest tremor and/or rigidity (Postuma et al., 2015), and by the underlying pathology of irreversible loss of dopamine in the basal ganglia (or striatum) of the brain. Dopaminergic cell loss occurs following degeneration of dopaminergic neurons in the substantia nigra (Kish et al., 2017). The characteristic motor symptoms that prompt diagnosis present at a relatively late stage in the pathological process. The term parkinsonism is distinct, and refers only to the clinical motor manifestations (bradykinesia, tremor, rigidity) (Postuma et al., 2015), that is, not specifying the underlying cause. These features may be

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attributable to PD or to other causes. That parkinsonism therefore comprises a broader category than PD is reflected in illness prevalence; the lifetime risk of parkinsonism is estimated at 4.4% for men and 3.7% for women (Elbaz et al., 2002), while that of PD is estimated at 2% for men and 1.3% for women (Elbaz et al., 2002).

PD is rare before the age of fifty (Twelves et al., 2003), but increasingly common with age (Poewe et al., 2017). The prevalence in those aged 65 and older is in the order of 2–3% (Poewe et al., 2017). Approximately 10% of cases have an identifiable genetic cause (Ascherio and Schwarzschild, 2016). In the remainder, referred to as 'idiopathic' PD, the pathogenic mechanisms are poorly understood.

Selective striatal dopamine deficiency is the hallmark feature of PD, together with the widespread accumulation of intracellular protein (α-synuclein) in intracellular inclusions known as Lewy bodies (Poewe et al., 2017). Over recent decades, however, it has become clear that PD pathogenesis is not limited to the dopaminergic system, but rather involves numerous cell types in both the central and the peripheral autonomic nervous systems (Poewe et al., 2017). Lewy pathology is observed early in both cholinergic and monoaminergic neurons in the brainstem and in olfactory system neurons, and more latterly, with disease progression, in the limbic system and neocortex (Poewe et al., 2017). A range of mechanisms and pathways have been implicated, including α-synuclein proteostasis, calcium homeostasis, oxidative stress, mitochondrial function, axonal transport, and neuroinflammation (Poewe et al., 2017). It appears that both behavioural and environmental effects modify the risk (Ascherio and Schwarzschild, 2016).

Drug-induced parkinsonism is the second most common aetiology of parkinsonism after idiopathic PD (López-Sendón et al., 2013). Drug-induced parkinsonism, relating to prescribed drug treatments, is a side effect most commonly associated with antipsychotic agents, but which can occur with a variety of other treatments including antidepressants, calcium channel antagonists, antiarrhythmic and antiepileptic drugs (López-Sendón et al., 2013). There is evidence that at least some of these drugs may cause neurotoxic damage to nigrostriatal dopaminergic neurons (Mena et al., 1995). Despite being considered reversible on drug discontinuation, suspected drug-induced parkinsonism renders as many as 25% of individuals subject to progressive or persisting parkinsonism (Marti Masso and Poza, 1996).

2. Evidence from preclinical and human studies

2.1. Evidence from preclinical studies: is there a plausible mechanism?

Striatal dopamine nerve terminal markers, including the dopamine metabolite, homovanillic acid, the striatal dopamine transporter, and the vesicular monoamine transporters (VMAT) are all observed at low levels in PD, indicating the hallmark deficiency of the dopaminergic system (Kish et al., 2017). The rate of dopaminergic neuronal loss is initially exponential: a study of neuronal loss in PD brains compared to that in ageing brains demonstrated 45% neuronal loss during the first decade of PD, ten times that accounted for by ageing (Fearnley and Lees, 1991). In some regions of the substantia nigra, average neuronal loss in PD exceeded 90% (Fearnley and Lees, 1991).

Methamphetamine and its metabolite amphetamine cause release of dopamine from dopaminergic neurons in the human brain (Laruelle et al., 1995). Evidence from animal studies using both histological techniques and dopamine marker measurement indicates that methamphetamine exposure induces structural damage in dopaminergic neurons (reviewed in Kish et al., 2017). Repeated, high-dose methamphetamine administration modifies the dopamine transporter, a possible mechanism in long-lasting dopaminergic deficits (Fricks-Gleason et al., 2016). In animal studies, dopamine synthesis may recover within six months of amphetamine exposure, indicating that at least some dopaminergic effects are reversible (Melega et al., 2008).

2.2. Evidence from human studies: is there a plausible mechanism?

Evidence from human studies is limited. There are reduced levels of striatal dopamine (Moszczynska et al., 2004; Wilson et al., 1996) and of dopamine markers, such as the dopamine transporter (McCann et al., 1998, 2008; Volkow et al., 2001a). Striatal dopamine levels reduced by up to 50% have been observed in chronic methamphetamine users (Wilson et al., 1996). Moszczynska et al. (2004) conducted one of very few studies examining, at autopsy, the basal ganglia of human chronic methamphetamine users. The study found prominent reductions in dopamine levels, which were greater in the caudate nucleus (61%), than the putamen (50%). This pattern differed to that observed in PD controls, in whom mean dopamine levels were more marked in the putamen (loss of 97%) than in the caudate (loss of 82%). The putamen and caudate are entailed in motor and cognitive function respectively, and it was posited that dopamine reduction in the caudate may explain cognitive impairment in some methamphetamine users, and that the relative sparing of the putamen might explain the absence of PD. There was considerable variability in the levels of dopamine loss observed. While several exhibited very severe dopaminergic deficiency, the authors concluded that, in the majority, the doses used recreationally would not give rise to significant irreversible damage to dopaminergic neurons (Kish et al., 2017). This was a small sample (n = 20), however, and there were no pre-mortem clinical characteristics reported. Of note, the methamphetamine users in the sample had a median age of 31 years with a modal 10 years' duration of use. It is unknown how many may have progressed to PD had they lived longer.

2.3. Evidence from preclinical studies: are the neurotoxic effects of methamphetamine irreversible?

The risk for PD increases with age, with continued progressive loss of dopaminergic neuronal integrity. If methamphetamine-related effects on dopaminergic neuronal integrity were chronic and irreversible, the baseline for dopaminergic function would be lower than in non-methamphetamine users. Thus, it is plausible that with progressive age-related loss of dopaminergic function, methamphetamine users will achieve prematurely the threshold of dopamine function loss required for clinical manifestation of parkinsonism. This prompts the question: does the observed dopaminergic neuronal integrity damage induced by methamphetamine use constitute permanent degenerative change or reversible modulatory effects?

Neuronal degeneration in animals is observed at high methamphetamine doses that exceed those of recreational use in humans (Woolverton et al., 1989), and thus may not be a good preclinical model of human methamphetamine abuse. There is insufficient evidence to answer the question whether recreational methamphetamine use in humans causes such irreversible loss of dopaminergic neurons (Kish et al., 2017). Binge-like dosing is more deleterious in animal models, with more severe or longer-lasting effects than comparable cumulative dosing over time (Moszczynska and Callan, 2017). Of note, prior methamphetamine exposure attenuates the later binge-induced striatal dopamine level decrease, perhaps indicative of tolerance to the neurotoxic effects of methamphetamine (McFadden et al., 2015). Nonetheless, evidence for a strong dose-dependent relationship between amphetamine use and neural toxicity has been demonstrated in a variety of animal species, including rodents and primates (Yamamoto et al., 2010).

2.4. Evidence from human studies: are the neurotoxic effects of methamphetamine irreversible?

Evidence from the neurocognitive literature is pertinent here. Reviews suggest that methamphetamine abuse is associated with mild cognitive impairment (Dean et al., 2013), which, in turn, is associated with effects on dopamine function (Volkow et al., 2001b). Importantly,

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