Parkinsonism and Related Disorders 25 (2016) 27–32

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

Adults with a history of illicit amphetamine use exhibit abnormal substantia nigra morphology and parkinsonism

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ARTICLE INFO

Article history:
Received 18 September 2015
Received in revised form
11 February 2016
Accepted 18 February 2016

Keywords:
Methamphetamine
Amphetamine
Substantia nigra
Parkinsonism
Transcranial ultrasound

ABSTRACT

Introduction: The sonographic appearance of the substantia nigra is abnormally bright and enlarged (hyperechogenic) in young adults with a history of illicit stimulant use. The abnormality is a risk factor for Parkinson's disease. The aim of the current study was to identify the type of illicit stimulant drug associated with substantia nigra hyperechogenicity and to determine if individuals with a history of illicit stimulant use exhibit clinical signs of parkinsonism. We hypothesised that use of amphetamines (primarily methamphetamine) is associated with substantia nigra hyperechogenicity and clinical signs of parkinsonism.

Methods: The area of echogenic signal in the substantia nigra was measured in abstinent human amphetamine users (n = 27; 33 ± 8 years) and in three control groups comprising a) 'ecstasy' users (n = 19; 23 ± 3 years), b) cannabis users (n = 30; 26 ± 8 years), and c) non-drug users (n = 37; 25 ± 7 years). A subset of subjects (n = 55) also underwent a neurological examination comprising the third and fifth part of the Unified Parkinson's Disease Rating Scale.

Results: Area of substantia nigra echogenicity was significantly larger in the amphetamine group (0.276 ± 0.080 cm^2) than in the control groups (0.200 ± 0.075, 0.190 ± 0.049, 0.191 ± 0.055 cm^2, respectively; $P < 0.002$). The score on the clinical rating scale was also significantly higher in the amphetamine group (8.4 ± 8.1) than in pooled controls (3.3 ± 2.8; $P = 0.002$).

Conclusion: Illicit use of amphetamines is associated with abnormal substantia nigra morphology and subtle clinical signs of parkinsonism. The results support epidemiological findings linking use of amphetamines, particularly methamphetamine, with increased risk of developing Parkinson's disease later in life.

1. Introduction

The substantia nigra (SN) is a midbrain structure with a high concentration of dopaminergic neurons. The sonographic appearance of the SN is abnormally bright and enlarged (hyperechogenic) in young adults with a history of use of multiple illicit stimulant drugs (amphetamine, methamphetamine, ecstasy, and/or cocaine) [1]. This observation has clinical significance because the abnormality is a well-established risk factor for Parkinson's disease. Healthy older adults with the abnormality are 17 times more likely to develop Parkinson's disease over a three year period [2].

The aim of the current study was to identify the type of illicit stimulant drug associated with abnormal SN morphology and risk of Parkinson's disease. We hypothesised that use of illicit amphetamine and/or methamphetamine ('amphetamines') is associated with SN hyperechogenicity, but that use of ecstasy or cannabis is not. We also hypothesised that individuals with a history of illicit amphetamine use would exhibit clinical signs of parkinsonism. Our hypothesis is based on several lines of evidence.

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http://dx.doi.org/10.1016/j.parkreldis.2016.02.019
1353-8020/

Use of amphetamines at recreational doses is toxic to dopaminergic neurons and retrospective analysis of hospital records suggest that methamphetamine use is associated with increased risk of developing Parkinson's disease later in life (2.65 hazard ratio) [3,4]. Furthermore, the brains of chronic methamphetamine users and Parkinson's disease patients both exhibit reduced dopamine reuptake transporters [3,5], and abnormal iron deposition and increased intracellular inclusions in the SN [6,7]. The results of the current study are important for the 14–56 million people (global estimate) with a history of recent use of illicit amphetamines and the provision and cost of future healthcare services [8]. Some of the ultrasound data has been published previously in a different form [1].

2. Methods

One hundred and sixteen subjects aged 18–50 years were recruited into the study via community advertisement. The target group comprised 27 individuals with a history of amphetamine and/or methamphetamine use (≥5 occasions; termed 'amphetamine' group) and the control groups comprised a) 19 individuals with a history of ecstasy use (≥5 occasions) but minimal use of amphetamines (<5 occasions; termed 'ecstasy' group), b) 31 individuals with a history of cannabis use (≥5 occasions) but no stimulant use (termed 'cannabis' group), and c) 39 individuals with no history of illicit drug use (termed 'non-drug' group). All experimental procedures were approved by the University of South Australia and Southern Adelaide Clinical Human Research Ethics Committees. Experimental procedures were conducted according to the Declaration of Helsinki and written informed consent was obtained.

2.1. Subject screening

Subjects underwent the following screening tests prior to participation: a) brief medical history questionnaire, b) urine drug test (PSCupA-6MBAU, US Diagnostics Inc., Huntsville, Alabama, USA), c) neuropsychological assessment involving Logical Memory I and II [9], Verbal Trails and Verbal Fluency [10,11], and Digit Span forwards and backwards [12], d) Beck Depression Inventory-II [13], e) Edinburgh Handedness Inventory [14], and f) drug history questionnaire to document recent and lifetime use of alcohol, tobacco, and illicit drugs. The drug history questionnaire listed 20 illicit drugs and requested information on other illicit drugs not listed. Items on the questionnaire included age of first use, age of regular use, duration of use, frequency of use (current and lifetime), average dose if known (current and lifetime), and time since last use for each drug and the number of drug overdoses.

Exclusion criteria included a) history of neurological damage and/or neurological illness prior to illicit drug use, b) use of antipsychotic medications, c) frequent illicit opioid use (>2 times per year during period of illicit drug use), and d) positive urine test for amphetamine, methamphetamine, 'ecstasy' (3,4-methylenedioxymethamphetamine), cocaine, opioids, and/or benzodiazepines. Subjects who returned a positive urine test for cannabis were allowed to participate if use was greater than 12 h prior to the experiment. This exemption was necessary because tetrahydrocannabinol can remain in the body for up to 80 days after last use [15].

2.2. Experimental protocol

Transcranial sonography was performed by one researcher (GT) using published methodology [1] and a Philips iU22 ultrasound system (manufactured June 2004, refurbished November 2011 with software level 6.0.2.144, Philips Healthcare, Best, Netherlands). A 1–5 MHz transducer (model s5-1, Philips Healthcare, Best, Netherlands) was positioned over the pre-auricular acoustic bone window located above the ear. The B-mode setting was used and the dynamic range and penetration depth were set at 60 dB and 14–16 cm, respectively. A qualitative rating of the bone window was made (1-excellent, 2-good, 3-poor, 4-very poor) and the area of echogenicity at the anatomical site of the SN was measured at its greatest extent according to international guidelines [16]. Other parameters that were measured include the internal diameter of the third ventricle, area of the red nucleus at its greatest extent (right and left side), and qualitative rating (normal, abnormal-interrupted, abnormal-absent) of the raphii nucleus (on the clearest side) [16]. Inter-rater reliability and reproducibility of the ultrasound procedure and operator has been previously published [1].

A subset of subjects (n = 55) also underwent a neurological examination performed by an experienced neurologist who specialises in movement disorders (RW). The neurologist was blinded to the subject's drug history and the examination involved the third and fifth part of the Unified Parkinson's Disease Rating Scale (UPDRS) [17].

2.3. Data analysis

Group data are presented as mean ± SD. Between-group comparison of subject characteristics, neuropsychological performance, and ultrasound parameters was made with one-way analysis of variance (ANOVA). One-way ANOVA was also used to compare a) cannabis use in the amphetamine, ecstasy, and cannabis groups and b) UPDRS Part III score in the three control groups (non-drug, ecstasy, and cannabis). Non-parametric data were transformed to ranks and ANOVA on ranks was performed. Post-hoc discrimination between means was made with Bonferroni procedure. Unpaired Student's t-test with sequential Bonferroni correction was used to compare a) use of ecstasy in the amphetamine and ecstasy groups and b) clinical data in the amphetamine and pooled control group. Pearson Product Moment or Spearman Rank Order correlation was used to investigate the relationship between area of SN echogenicity and subject characteristics, drug–use parameters, and clinical parameters (SigmaPlot Version 11.0, Systat Software Inc, San Jose, USA). Significance was set at $P < 0.05$.

3. Results

3.1. Subject characteristics

Three subjects were excluded due to insufficient bone window for transcranial sonography. Table 1 shows the characteristics for the remaining 113 subjects. The groups significantly differed in age ($F_{3,112} = 13.313$, $P < 0.001$). The average age of the amphetamine group was 6–10 years older than the other groups ($P < 0.001$). This was expected given that the onset of cannabis and ecstasy use tends to occur at an earlier age than amphetamine use. The groups did not differ in years of education, hand dominance (laterality quotient), or neuropsychological performance. The groups tended to differ in recent symptoms of depression (BDI-II score), but the effect did not reach statistical significance ($P = 0.053$). Thirteen subjects across the drug-using groups had received a formal diagnosis of depression after commencement of illicit drug use (three-cannabis, three-ecstasy, seven-amphetamine) and two were currently medicated (one-cannabis, one-amphetamine).