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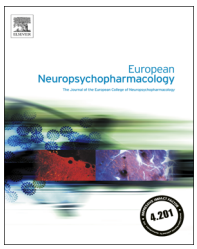

Monoaminergic dysfunction in recreational users of dexamphetamine

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Abstract
Preclinical studies suggest that dexamphetamine (dAMPH) can lead to monoaminergic neurotoxicity. This exploratory study aimed to investigate effects of recreational dAMPH use on the dopamine (DA) and noradrenaline (NA) systems in humans. To that purpose, eight male abstinent dAMPH (26.0±4.0 years) users and 10 age- and IQ-matched male healthy control subjects (23.0±3.8) underwent neuropsychological testing sensitive to DAergic function and single photon emission computed tomography (SPECT) scanning with [^{123}I]FP-CIT to determine striatal DA transporter (DAT) binding. In addition, changes in cerebral blood flow (CBF) induced by the DA/NA reuptake inhibitor methylphenidate (MPH) were measured using pharmacological magnetic resonance imaging (phMRI). Performance of dAMPH users was significantly worse on executive function and verbal memory tasks. Striatal DAT binding ratios were on average lower in dAMPH users (near-significant, p=0.05). In addition, CBF in control subjects decreased significantly in response to MPH in gray matter and basal ganglia, among which the striatum, thalamus and hippocampus by 10% to 29%. However, in dAMPH users the CBF response was blunted in most brain areas studied, only decreasing in the hippocampus and orbitofrontal cortex. When comparing groups, CBF response was found to be significantly different in the thalamus with a decrease for healthy controls and a blunted response in dAMPH users. Collectively, our findings of a blunted hemodynamic response in monoaminergic regions, in combination with indications for lower striatal DAT binding and poorer behavioral measures are likely to represent DAergic dysfunction in dAMPH users, although NAergic dysfunction may also play a role.

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1. Introduction

The dopaminergic (DAergic) system plays a pivotal role in many different neurological and neuropsychiatric disorders, such as Parkinson's disease, schizophrenia and attention deficit hyperactivity disorder (ADHD) (for review (Missale et al., 1998)). Consequently, many drugs have been developed, that act on the dopamine transporter (DAT) or dopamine receptors. Of these drugs, dexamphetamine (dAMPH) is prescribed for the treatment of ADHD, but is also frequently used in recreational settings. Preclinical studies in non-human primates however, have indicated that even clinically relevant doses of dAMPH can lead to damage of nerve terminals of DAergic neurons: the concentration of striatal DA, the DAT density and vesicular monoamine transporter (VMAT-2) sites were significantly reduced after dAMPH administration (Ricaurte et al., 2005). Although some positron emission tomography (PET) studies reported loss of striatal DAT in methamphetamine (METH) users (McCann et al., 1998, 2008), little is known about the effects of recreational dAMPH use on the DA system in human users. To our knowledge, only one study has previously investigated the effects of dAMPH in the human brain. In this study reductions in striatal DAT binding were observed using single photon emission computed tomography (SPECT) (Reneman et al., 2002) in combined ecstasy and dAMPH users versus sole ecstasy users. Because DA is involved in many important neurobehavioral functions, such as executive and motor function, attention and inhibition, it is important to study the potential consequences of dAMPH-induced neurotoxicity (Van den Heuvel and Pasterkamp, 2008).

The purpose of the current study was to investigate the effects of recreational dAMPH use on the DAergic system using SPECT and a relatively novel MRI imaging technique, called pharmacological MRI (phMRI), to assess DA (dys)function. phMRI indirectly determines monoaminergic function by looking at the hemodynamic response to a pharmacological challenge (Ogawa et al., 1990). Neurotransmitter-specific drug challenges can evoke changes in synaptic activity, and resultant alterations in metabolic demand, requiring changes in cerebral blood flow (CBF) and/or cerebral blood volume (CBV) as a result of neurovascular coupling (Jueptner and Weiller, 1995). For instance, Jenkins and co-workers (Jenkins et al., 2004) have shown that phMRI adequately assesses DA dysfunction, as dAMPH-induced hemodynamic changes correlated well with loss of DAT densities measured in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-lesioned parkinsonian primates, using PET. Interestingly, a recent imaging study showed a reduced amphetamine-induced DA release in cocaine users (Martinez et al., 2007). In addition several behavioral studies have linked DAergic dysfunction to deficits in attention, memory and executive function (for review (Robbins and Arnsten, 2009)).

In this explorative study, we assessed brain monoamine function in dAMPH users and comparison subjects, by examining the hemodynamic response to an acute oral challenge with methylphenidate (MPH). MPH is a DAT blocker causing increased levels of synaptic DA, although it also seems to have effects on norepinephrine (NE) levels, by blocking also the NE transporter (NET) (Hannestad et al., 2010; Volkow et al., 1998). We hypothesized that dAMPH users would have lower striatal DAT binding levels than controls and a blunted hemodynamic response to MPH. We also predicted that dAMPH users would show an altered performance on tests of attention, memory and executive function.

2. Experimental procedures

2.1. Study procedure

Participants underwent phMRI with an oral MPH challenge, followed by [^{123}I]FP-CIT SPECT scanning (to measure DATs) 1–3 weeks later. In addition, neuropsychological tests and questionnaires were administered on the day of the SPECT scan.

2.1.1. Subjects and study design

The medical ethics committee of the Academic Medical Center in Amsterdam approved the study procedures. Participants were recruited by advertising on the medical campus, websites and in newspapers. They received a small financial compensation of 50 euros per assessment day.

Eight male, recreational users of dAMPH and 10 male, healthy control subjects (matched for age and IQ) participated. Written informed consent was obtained from all subjects. The eligibility criterion for the dAMPH group was previous use of dAMPH on more than 40 occasions. The cut-off point was based on previous studies from our group, where lower striatal DAT binding was found in ecstasy users with combined dAMPH use (Reneman et al., 2002). The control subjects were healthy subjects with no self-reported prior use of dAMPH.

Subjects were asked to refrain from using caffeinated products on assessment days. In addition, both controls and dAMPH users agreed to abstain from all psychoactive drugs for at least 2 weeks before scanning sessions. They underwent urine drug screening on assessment days (with an enzyme-multiplied immunoassay for amphetamines, cocaine, cannabis, alcohol, opiates and benzodiazepines). Exclusion criteria were: self-report of neuropsychiatric diagnosis, history of brain disease or injury, use of medication influencing the DAergic system (e.g., methylphenidate), a positive urine-screen for amphetamines or any contra-indication to MRI.

2.1.2. Behavioral tests

The Dutch Adult Reading Task (DART) was used to estimate IQ (Schmand et al., 1998). The DART is the Dutch counterpart of the National Adult Reading Test (Nelson, 1982). It is relatively insensitive to cognitive deterioration due to neurologic disorders and was used to evaluate the premorbid IQ.

We selected five domains sensitive to DAergic function: executive function, attention, memory, mood and impulsivity. Tests were administered in a mixed balanced order, with questionnaires presented during the recall part of the RAVLT, to ascertain that no other tasks of a verbal nature (e.g. DART) would interfere.

Executive function was measured using the trail making test. Part A of this test (TMT-A), in which the subject draws lines connecting consecutive numbers spread randomly on the page, tests both visual scanning and motor speed (Reitan, 1956). Part B of this test (TMT-B) alternates numbers with letters, focusing more on executive function and visuomotor tracking. The ratio of times to complete both parts of the test (TMT-B/TMT-A) was calculated to assess executive function taking individual differences in visual scanning and motor speed into account.

The sustained attention to response task (SART) displays numbers one through nine randomly, followed by a mask and cue. The subject needs to respond to the cue, except when the number three appears (Bellgrove et al., 2005). The mask insures that speed-accuracy trade-offs are of no major influence on the outcome. Response variability was calculated (standard deviation go