Differentiation Of Dopaminergic From Noradrenergic Neurobehavioral Effects Of Stimulants

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Background

- While stimulants have therapeutic value in attention-deficit and sleep disorders, the use of stimulants may lead to addiction and related issues.
- Most likely the subjective and psychological effects of the stimulants, lead to craving for the substance in humans who are vulnerable to develop addiction to stimulants. (Bigelow and Walsh, 1998).
- Amphetamine, but not phentermine, produced central dopamine release in baboons (Alexander, *et al.,* 2005).

Objective

- To determine if pharmacological doses of phentermine will increase the intrasynaptic release of norepinephrine (NE), but not dopamine (DA), in the living human brain
- To determine if the acute oral administration of pharmacological doses of phentermine will increase intrasynaptic release of NE, but not DA
- To determine if the subjective effects of stimulants can occur in the absence of the intrasynaptic release of DA

Methods

Phentermine challenge study

- Four healthy adult human subjects ranging in age from 22-29 years
  - 2 men
  - 2 women
- Magnetic resonance imaging (MRI) scan for co-registration with the PET scans
- Positron emission tomography (PET) scans for 90 min each after the intravenous administration of 740 MBq (20 mCi) [^{11}C]raclopride (a DA receptor ligand).
- Five min before the first dose of [^{11}C]raclopride
  - An oral placebo in a single-blind format
- 90 min PET scan
- Fifteen min before the second dose of [^{11}C]raclopride
  - An oral dose of 30 mg of phentermine in a single-blind format
- 90 min PET scan

Amphetamine challenge study

- Eighty six different healthy adult human subjects ranging in age from 18 to 30 years,
  - 50 Men
  - 36 Women
- Magnetic resonance imaging (MRI) scan for co-registration with the PET scans
- Positron emission tomography (PET) scans for 90 min each after the intravenous administration of 740 MBq (20 mCi) [^{11}C]raclopride (a DA receptor ligand)
- Five min before the first dose of [^{11}C]raclopride
  - 10 mL 0.9% NaCl IV bolus over 2-3 minutes
- 90 min PET scan
- Five min before the second dose of [^{11}C]raclopride
  - 0.3 mg/kg amphetamine IV bolus over 2-3 minutes
- 90 min PET scan

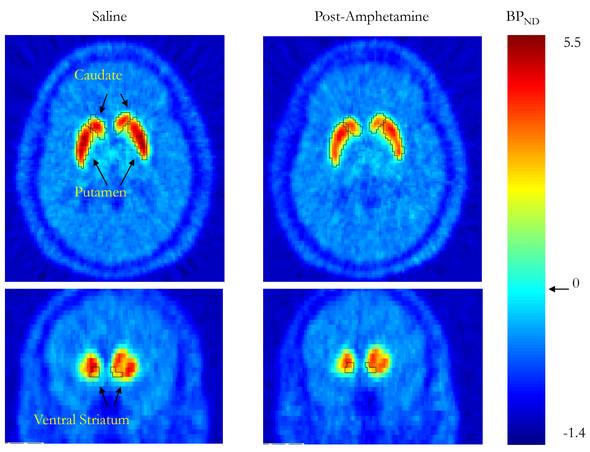


Figure 1. Representative trans-axial (top row) and coronal images (bottom row) of parametric nondisplaceable (BP_{ND}) volumes, baseline saline (left panel) and post-amphetamine (right panel) scans taken from one subject (Male, 20 years). Outlines of volumes of interest (VOIs) for the caudate nucleus, putamen, and ventral striatum are shown. Color scale bar indicates voxel BP values which can assume negative values in cerebrospinal fluid (CSF) space and outside the brain (Munro, *et al.*, *Biological Psychiatry* 2006; 59: 966-974).

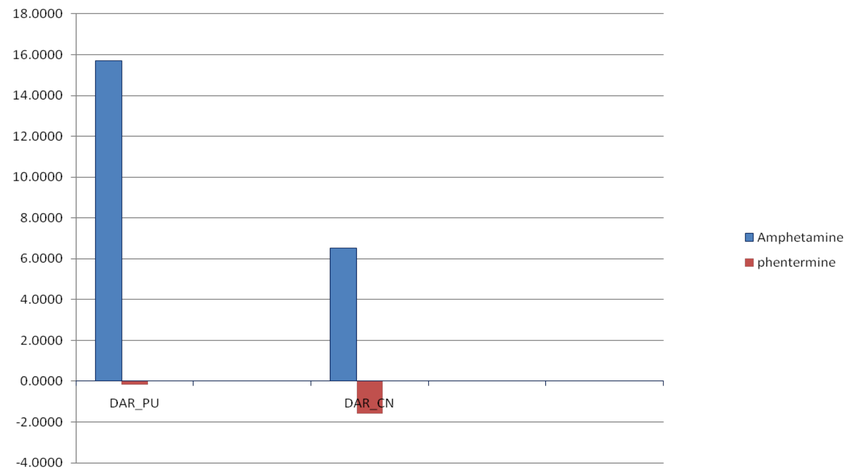
Methods (cont.)

Dopamine release (DAR)

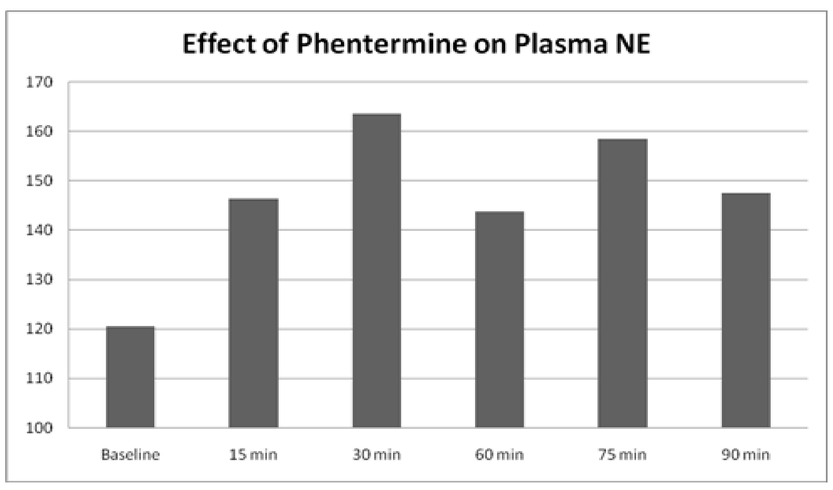
$$(DAR) = \frac{BP_{ND\ saline} - BP_{ND\ amphetamine}}{BP_{ND\ saline}}$$

BP_{ND} = nondisplaceable binding potential

Striatal dopamine release (DAR) in healthy adults administered amphetamine or phentermine



Dopamine release (DAR) in the putamen (DAR_PU) and caudate nucleus (DAR_CN) induced in healthy adults by amphetamine (blue) is significantly greater > than phentermine (red).



Conclusions

- Dopamine release (DAR)
- Negligible with phentermine
  - Humans (Current study)
  - Baboons (Alexander, *et al.,* 2005)
- Marked with amphetamine
  - Humans (Munro, *et al.,* 2005)
  - Baboons (Alexander, *et al.,* 2005).
- Norepinephrine release may contribute to the amphetamine-like subjective effects of stimulants (Rothman, *et al.,* 2001).
- Differentiation of the dopaminergic from the noradrenergic contributions of cocaine and other like stimulants may facilitate the development of interventions focused to the behavioral effects.
- These results will likely facilitate novel interventions for stimulant addiction.

Acknowledgements

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