PET studies of ephedrine and pseudoephedrine

Y.-S. Ding[1], M. Mueller[2], M. Schwaegler[2], D. Alexoff[1], F. Roesch[2], J.S. Fowler[1], N.D. Volkow[1]
[1]Brookhaven National Laboratory, Chemistry Department, Bldg. 555, Upton, NY, USA 11973.
[2]Institut für Kernchemie, Johannes Gutenberg-Universität Mainz

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Introduction:
Ephidrine (EPH, common name "Ephedra") and pseudoephedrine (PEPH) are widely available in asthma, ophthalmic, cold and allergy and weight-loss (so-called "fat-burning") products, and they are found in more than 100 pharmaceutical formulations. However, animal studies and human clinical evaluation of ephedrine neurotoxicity indicated that multiple doses of the dietary supplement ephedrine can cause severe hyperthermia and modest dopamine depletions in the brain. Moreover, because these drugs have reinforcing effects and are self-administered by laboratory animals there is concern that they may be diverted for abuse. Currently, a bill to ban the sale of all products that contain ephedrine is proposed, under the assumption that ephedrine, the chief active ingredient in many popular weight-loss, body-building and energy boosting products, has led to hundreds or thousands of deaths nationwide. The U.S. armed forces have now banned "ephedra" products from commissaries and military exchanges worldwide because it has been linked to heart attacks, strokes and seizures. Yet we know very little about the effects of these drugs in the human brain and the consequences of chronic treatment. It is therefore crucial to better understand how these two drugs behave in living systems.

Methods:
We have currently labeled EPH and PEPH with carbon-11 by reacting the norprecursor (compound without the N-methyl group) with [^{11}C]CH_3I, and initiated PET and MicroPET studies to determine their biodistribution and pharmacokinetics in the baboon and rodent brain. Binding specificity in vivo was accessed by blocking studies with the parent compound and specific blockers. Plasma assays for the presence of unchanged labeled tracers were carried out using both HPLC and solid phase extraction methods.

Results:
The distribution of [^{11}C]EPH and [^{11}C]PEPH in the baboon brain was heterogeneous with the highest uptake occurring in the basal ganglia (BG, average 0.025% of the injected dose/cc) and lowest in frontal cortex (FC) and cerebellum (CB). The BG/CB ratio was about 1.4-1.6 for both tracers. The time required to reach the peak brain uptake was approx. 30 min. The results of the assays for unchanged tracer in baboon plasma after IV injection of [^{11}C]EPH and [^{11}C]PEPH were similar, with 75-85% at 30 min and 60-70% at 60 min remaining unchanged. Pretreating baboons with unlabeled EPH or PEPH prior to tracer injection significantly altered the blood flow, resulting in increased uptake of the radiotracers as compared to the baseline.

Summary:
The high uptake of EPH and PEPH in striatum (where the nucleus acccumbens, which is the brain region associated with the reinforcing effects of abuse, is located) is compatible with their reinforcing effects in laboratory animals. However, their relative slow brain uptake as compared to that of cocaine or of methylphenidate (whose brain uptake peaked at <5 min and at 8-10 min respectively) suggests that they will be less reinforcing than these stimulant drugs. We are currently also investigating their binding specificity in brain and peripheral organs. It has been speculated that ephedrine may cause deaths, heart attacks and strokes, which is consistent with our observation that these two drugs significantly alter blood flow in living systems. This places a sense urgency to better understand their physiological role in humans. We believe these new pharmacological properties as well as their potential side effects including those of abuse. These studies set the stage for future investigation of the drug effects in human.

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