Psychopharmacology (2010) 209:383–394
DOI 10.1007/s00213-010-1809-8

ORIGINAL INVESTIGATION

Smoking produces rapid rise of [^{11}C]nicotine in human brain

Marc S. Berridge · Scott M. Apana · Kenichi K. Nagano · Catherine E. Berridge · Gregory P. Leisure · Mark V. Boswell

Received: 1 October 2009 / Accepted: 17 February 2010 / Published online: 16 March 2010

Abstract
Rationale Variation in the rate at which drugs reach the brain influences many different drug effects and is also thought to influence liability to addiction. For example, rapid intravenous delivery of cocaine and nicotine is more effective in producing hedonic effects, tolerance, psychomotor sensitization, and in inducing gene expression. Smoking is thought to result in an especially rapid rate of rise of nicotine in the brain, but whether this is true has never been adequately addressed. Thus, in this study, we sought to determine the true rate of rise of smoked nicotine in human brain and compare this with previous intravenous nicotine delivery.
Methods Positron emission tomography scans of lung and brain regions and arterial and venous blood curves were obtained in human subjects after single puffs from cigarettes formulated with [^{11}C]nicotine.
Results The rise of nicotine concentration following a single puff was rapid, reaching more than 50% of maximum brain levels within 15 s of bolus arrival in the brain in most subjects. This rate of rise was considerably faster than that seen in previous studies using intravenous administration.
Conclusions Uptake in human brain from a single inhalation was sufficiently rapid that it is plausible that fast rate-of-rise contributes to nicotine dependence in smokers.

Keywords Nicotine · Addiction · Pharmacokinetics · Cigarettes · Positron tomography

Introduction

Effects of many drugs, including nicotine, vary as a function of how rapidly the concentration of the drug increases in the brain tissue ("rate of rise"), independently of peak drug concentrations (de Wit et al. 1992; Ferrario et al. 2008; Nelson et al. 2006; Samaha et al. 2005; Schneider et al. 1996; Spencer et al. 2006; Volkow et al. 1995). For example, for potentially addictive drugs, more rapid rates of rise produce more intense hedonic (euphorigenic) effects (Abreu et al. 2001; Comer et al. 1999; Cone 1995; de Wit et al. 1992; Evans et al. 1996; Henningfield and Keenan 1993; Kollins et al. 1998; Marsch et al. 2001; Resnick et al. 1977). Imaging studies have related this to the rate of rise of both methylphenidate (Spencer et al. 2006) and cocaine in the brain (Gatley et al. 1995, 1997; Volkow et al. 1990, 1994, 1995, 1996a, b, 1997, 1999). With repeated administration, rapid rise rates have been associated with greater tolerance of some effects (Cleton et al. 1999) and with greater sensitization of other effects, in particular, the psychomotor effects of cocaine and nicotine (Samaha et al. 2004, 2005; Samaha and Robinson 2005). The reason that rate of drug entry into the brain influences behavioral and psychological effects is presumably because it alters their physiological impact. Indeed, rate of rise is reported to

M. S. Berridge (✉) · S. M. Apana · K. K. Nagano · C. E. Berridge
3D Imaging LLC,
Cyclotron Suite Rm PS010,
UAMS Radiology #556, 4301 W. Markham St.,
Little Rock, AR 72205-7199, USA
e-mail: MBerridge@3DImagingLLC.com

M. S. Berridge
Departments of Radiology and Pharmaceutical Sciences,
University of Arkansas for Medical Sciences,
Little Rock, AR, USA

M. S. Berridge · C. E. Berridge · G. P. Leisure · M. V. Boswell
Case Western Reserve University,
Cleveland, OH, USA

influence a number of physiological effects of drugs (Abreu et al. 2001; Cone 1995; Gourlay and Benowitz 1997; Nelson et al. 2006) including on brain temperature (Brown and Kiyatkin 2005) and on induction of immediate early genes in a number of brain regions (Samaha et al. 2004, 2008). Interestingly, the effect of varying the rate of cocaine delivery on psychomotor sensitization and gene expression is not accompanied by variation in peak dopamine overflow in the striatum (Ferrario et al. 2008). As indicated above, there are many potential reasons why the rapid entry of drugs into the brain may increase susceptibility to addiction (de Wit et al. 1993; Gorelick 1998; Hatsukami and Fischman 1996; Samaha et al. 2004; Ungerstedt and Arbuthnott 1970; Wakasa et al. 1995). Smoking may be particularly effective to achieve fast rates of rise for several drugs, including nicotine. There is some anecdotal support for the hypothesis that smoked drugs are generally more abused than other forms, and it has been posited that smoking cigarettes produces a particularly rapid rate of rise of nicotine in the brain (Henningfield et al. 1993, 2000; Henningfield and Keenan 1993; Rose et al. 1999, 2007; Samaha et al. 2005; Samaha and Robinson 2005; Stitzer and de Wit 1998). Conventional nicotine pharmacokinetics have been measured (Gourlay and Benowitz 1997; Henningfield et al. 1993; Henningfield and Keenan 1993; Rose et al. 1999; Spencer et al. 2006) and so have brain kinetics after intravenous delivery of [^{11}C]nicotine (Muzic et al. 1998; Nordberg et al. 1989, 1990, 1995; Nybäck et al. 1994), after inhalation with a vapor inhaler (Bergstrom et al. 1995; Lunell et al. 1996) and after nasal administration (Schneider et al. 1996). However, data for kinetics and rate of rise in brain tissue after smoked nicotine delivery are lacking and may be different from data previously measured following other methods of administration. Therefore, the goal of this study was to provide the cerebral kinetics of smoked nicotine and to measure the rate of rise of nicotine produced by a single smoked cigarette puff.

Measures of the delivery kinetics of smoked nicotine in the human brain will be crucial to determine if the rate of rise is sufficiently fast to contribute to any of the above-mentioned mechanisms that have been implicated in human dependence upon cigarette smoking (Henningfield and Keenan 1993). To accomplish this, we used methods for nicotine synthesis and formulation and for positron emission tomography (PET) scanning of inhaled formulations, as described previously (Berridge et al. 1998, 2000, 2003; Lee et al. 2000, 2001; Lee and Berridge 2002; Muzic et al. 1998), and cigarettes radiolabeled with racemic [^{11}C]nicotine (Apana and Berridge 2010) to perform PET scans after bolus administration of nicotine by smoking. Thus, we quantified the uptake slope of the brain curve to determine the rise time, defined here as the time required for the nicotine concentration in the brain to rise from 20% to 80% of the maximum level that occurs immediately following the inhalation. The latency and the time required for the concentration rise can be compared to rates that others have previously reported to correlate with various drug effects.

It is important to note that the goal of this work was primarily to assess the temporal shape of the kinetic curve in the human brain to determine the rate of rise of nicotine after a single naturalistic puff. We chose to assess the curve that results from a single puff of a cigarette, as opposed to the sequence of puffs required to smoke a whole cigarette, in order to isolate the rise from a discrete pharmacological pulse, analogous to an intravenous bolus. Further, data from a single puff are more reproducible and more easily generalized to a series of inhalations than from a puff sequence, which would require deconvolution analysis. A measured brain curve from a simple one-puff administration can be used both to calculate the curves that would result from more complex administrations and to compare to data from other studies. Thus, PET scans of the lung and brain were acquired from independent single-puff nicotine administrations. During the PET scans, [^{11}C]nicotine in arterial and venous blood was measured. This experiment tests the hypothesis that the rate of rise of nicotine in the brain after a single puff is rapid enough, in comparison to previous reports, to affect the neuropharmacology and behavioral psychology of smoking.

Materials and methods

Subjects

Twelve healthy subjects (five females and seven males) were recruited for the study, in accordance with procedures approved by the Case Western Reserve University IRB, RDRC, and radiation safety committee. The average age was (mean ± SD, range) 26±8, 19–47 years; mean body weight was 150±29, 120–200 lb. Subjects were required to be smokers, but there were no criteria for amount of smoking. Subjects reported smoking 16±11, 3–40 cigarettes per day and reported that they had smoked for 7.6± 8.8, 1–30 years. All subjects reported that they smoked daily, that they considered themselves "addicted" to cigarettes, and during the study, uniformly exhibited a strong desire to smoke as soon as possible within the study restrictions. Informed consent was obtained. Race and gender were not criteria for selection or exclusion. Enrollment criteria were age 18 years or above, normal physical exam including nasal mucosa, normal blood and urinalysis results, no concomitant medications or history of respiratory, cardiovascular, neurologic, hepatic, or renal disease. Females had negative pregnancy tests or acceptable substitute. One female (S11) withdrew from the study because of personal reluctance. She was screened but did

not report on the scan day, was not replaced, and her data are not reported here. Smoking on the day of the study was not permitted from midnight until after acquisition of the brain scan. Most subjects reported that they felt immediate hedonic effects from the inhalations used to acquire the PET scans such as they normally experienced from smoking, variously described as lightheadedness, tingling, relaxed feeling, or an effect on heart rate. There were no reported or observed adverse events during the study.

Nicotine administration

Carbon-11 labeled nicotine was prepared, formulated, and administered as previously reported (Apana and Berridge 2010). Briefly, racemic nicotine was radiolabeled by methylation of racemic nornicotine with labeled methyl iodide. Racemic nicotine was used rather than the naturally occurring L(−) enantiomer. This was justified by our prior observations indicating that racemic nicotine is likely to provide the same result as optically resolved nicotine (Muzic et al. 1998). Those observations indicated that the contributions of receptor interaction to the uptake of L(−)-nicotine in brain tissue are small and difficult to detect, such that nicotine uptake does not depend to a significant extent on receptor concentrations. By contrast, the goal of this study was to measure gross biodistribution kinetics, which do not depend on stereospecific mechanisms, and so can be effectively measured with racemic nicotine. The choice of racemic nicotine was motivated by an extremely limited supply of the optically pure nornicotine precursor that is necessary to produce radiolabeled L(−)-nicotine.

A 10-mm length of cigarette was prepared labeled with [^{11}C]nicotine and installed in the apparatus for single-bolus administration (Fig. 1). An investigator held a flame near the tobacco as the scan acquisition was started. On instruction, the subject inhaled in his or her own normal smoking fashion, drawing the flame to light the tobacco and administering the nicotine dose as a bolus in one inhalation. Instructions were to inhale on command for the coordinated lighting and administration. There were no instructions concerning rate or duration of the inhalation, except that it be as similar as possible to the subject's normal smoking inhalation. Subjects were free to breath hold if that was their normal smoking procedure. The inhalation topography was not controlled or specifically measured. All subjects expressed a "need" to smoke at the time of the study. As the subject exhaled, the apparatus collected residual nicotine from the exhalation, from the slipstream smoke, and remaining on the cigarette fragment (Apana and Berridge 2010). Total residual nicotine was decay corrected and subtracted from nicotine initially deposited on the cigarette to calculate the administered radiation dose.

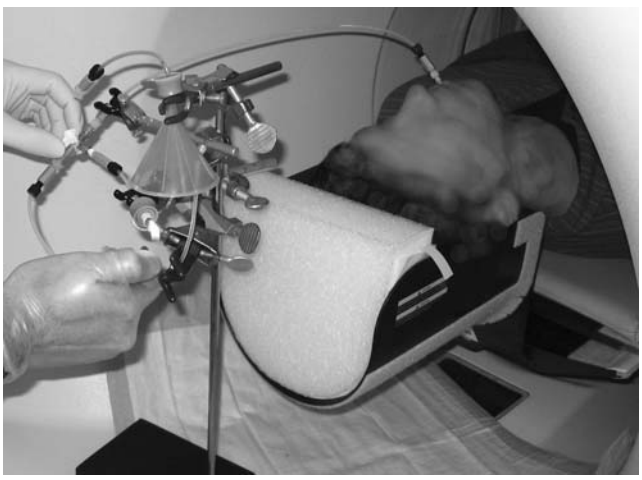

Fig. 1 Positron emission tomography scan in progress, showing apparatus for smoked administration of [^{11}C]nicotine. Subject face has been blurred to protect identity

PET scanning

Subjects were scanned in groups of four on each scan day. Scans were performed on a weekend day, beginning in the morning, with all subjects to be scanned that day arriving at one time. On arrival, subjects confirmed compliance with smoking restrictions. After arrival and review of consent and procedures, the subjects were prepared for the study by insertion of a venous catheter in one arm or hand and an arterial catheter in the opposite radial artery at the wrist. They were asked to practice using the study apparatus without lighting a cigarette. Fiducial markers were placed on the head for future image alignment, near the ears just anterior to the pinna, and one between the eyes at the bridge of the nose. They were placed with reference to anatomic and indelible marker landmarks and photographs made at the time of placement of fiducial markers for the magnetic resonance imaging (MRI) brain scans that were done of each subject within 1 week prior to the PET scans. The MRI scans were performed to provide anatomic landmarks for region of interest creation in the brain. Each subject was scanned twice in supine position, allowing time between scans for decay of carbon-11 (20.4 min half-life). The brain scan was performed before the lung scan because regional cerebral kinetics was of most interest and also to obtain cerebral kinetic data without any possibility of a confounding pharmacological effect of a prior administration on the brain. If a subject's first administration was unsuccessful, the second scan repeated the brain scan attempt. Otherwise, the lung was scanned with the field of view centered at the estimated position of the main bronchial bifurcation.

Four cigarettes were radiolabeled, one each of the preferred brand of each subject. For brain and lung scans, the method was the same except for camera position. The

first subject was positioned in the GE Advance PET scanner. A 3-min attenuation scan was performed. Then, the blood withdrawal for arterial and venous sampling was begun. Each catheter was connected to a Harvard syringe pump set to withdraw at 6 ml/min. The tubing was routed through heavily shielded blood radioactivity monitors (Muzic et al. 1997; Nelson et al. 1990; Rexon components, Cleveland, OH, USA) acquiring blood radioactivity data at 0.1-s intervals. Within 10 s of starting the blood monitors, the PET scanner was started, and then within 1–3 s, the subject inhaled the nicotine dose by smoking (Fig. 1). A 15-min dynamic scan sequence was used: 12 frames of 10, 9×20, and 20×30 s. Blood withdrawal and monitoring was nominally continued for 5 min, for a total withdrawn blood volume of 120 ml per subject. However, in practice, blood withdrawal was stopped when a post-bolus baseline in the blood was established, usually after less than 2 min. At the end of an acquisition from one subject, the next subject was immediately positioned and scanned in the same manner. In this way, four subjects were scanned at intervals averaging 19.5 min, completing four scans within 80 min.

A second synthesis of [^{11}C]nicotine, requiring 1 h, was performed during the first set of PET scans. A second set of four cigarettes was formulated shortly after completion of the first scans. A second set of PET scans was then obtained in the same manner, with subjects scanned in the same order as the first. The interval between scans for each subject averaged 91 min or 4.4 half-lives of carbon-11.

Data analysis

PET brain images were aligned with the MRI brain scans of each subject using semi-automated alignment techniques. MRI scans were used to identify regions of interest on the aligned image set, with the assistance of a physician certified in nuclear medicine. Regions of interest created on the scans for PET uptake quantification were whole brain, thalamus, cerebellum, sublenticular region (including ventral striatum [nucleus accumbens], ventral pallidum, parts of the extended amygdala macrosystem, and substantia innominata), amygdala, cingulate cortex, prefrontal cortex, and visual cortex. These regions were measured separately because of the possibility of regional kinetic differences. The lung distribution, similarly, was examined for regional differences (central, mid, and outer lung as defined on PET images). When no regional differences in kinetics were noted in lung or brain, data was analyzed by using a single whole-organ region of interest for each subject. The whole-brain region included the entire brain, and the whole-lung region included the observed portion of the lung in a 15-cm axial section to the chest walls, approximately centered on the main bronchial bifurcation, excluding the central region (trachea to first bifurcation, esophagus, and heart). From these defined regions and the dynamic PET scans, decay-corrected [^{11}C]nicotine activity present in each region was measured. Raw uptake values were adjusted using the measured administered dose and body mass of each subject to give uptake in units of standard uptake value (SUV: unitless fractional activity uptake per fractional body mass).

Terminology

The "rate of rise" refers to the rate at which a substance concentration increases in the brain, which could be conceived as the slope of the brain tissue concentration curve. However, similar phrases are sometimes used to mean the latency or time delay from the moment of administration until the drug reaches the brain. Latency, as opposed to slope, includes an interval during which the tissue concentration remains at zero before beginning to rise. This interval is the transit time for the bolus to move through the blood circulation to the brain from the point of administration. Here, we distinguish between these two periods and focus especially on the slope of the rising tissue curve, as the temporal factor likely to have the greatest impact on brain neurobiology and psychological function. Therefore, herein, the terms "latency" or "lag" are used to refer to the time delay from administration to the arrival of the substance in the tissue. We define the "rise time," as the time in seconds for a concentration curve to rise from 20% to 80% of its maximum value. This definition allows an objective measure related to the rate at which the nicotine concentration rises in tissue. In practice, for the purpose of measuring the rate of rise, a zero time for rise was designated to occur at the moment that the concentration of nicotine in the tissue (blood or brain) equaled 20% of the maximal value that it reached in that tissue during that trial. This initiation point was chosen because it could be unambiguously identified near the beginning of the rise of nicotine concentration above the baseline. This time point always occurred within a lag time of 15 s of the cigarette puff, and for six of nine subjects, the 20% threshold occurred within a lag time of 8 s from the cigarette puff. A second moment was chosen near the finish of the concentration rise. This was the moment when the brain concentration equaled 80% of the maximal value. The "rise time" was calculated as the time in seconds required for the concentration to rise between these two values, from 20% to 80% of the maximum value. The rise time was therefore a relatively objective measure of the parameter that we expect to have the greatest impact on brain function. That is, it captures the rate of change from low near-baseline concentrations of a drug to high near-maximal concentrations within a brain structure that mediates the drug's

effects and minimizes the effects of signal noise and of features of the curve shapes other than the rate of rise.

Results

Administration

The total administered dose per subject was limited by the approved IRB and RDRC applications to 12 mCi over two administrations, although the effectiveness of administration was variable (actual, 170–432 MBq; mean, 340; 4.6–11.7 mCi; mean, 9.2). Cigarettes for the experiment were formulated with 330±110 MBq (9±3 mCi) of [^{11}C]nicotine (Apana and Berridge 2010). After administration, the acidic smoke trap contained 44±30 MBq (1.2±0.8 mCi), representing exhaled plus slipstream nicotine. The cigarette stub contained 77±33 MBq (2.1±0.9 mCi) of residual nicotine. Measured administration was 30% to 80% of the dose placed on the cigarette, average 60%. The dose on a subject's second cigarette was adjusted based upon measurements of the first. The range of individual doses was 55–270 MBq, average 185 MBq (1.5–7.4 and 5 mCi).

It was anticipated and found that there would be instances of insufficient administered dose to produce suitable PET images because of the novelty of the methods necessary for administration of nicotine by smoking. This was a consideration in the choice to enroll 12 subjects in the study. Variability in dose administration was mainly due to incidents that reduced drug delivery, such as coughing, abnormally shallow inhalation, failure of inhalation timing, etc. and were a result of unfamiliarity of the scan and smoking procedures. Although practice sessions were held with the smoking apparatus, in hindsight, additional practice would have been beneficial. Subjects generally agreed that smoke delivered through the inhalation device was more “harsh” or “strong” than their usual cigarettes even though each person's preferred brand was used. This was almost certainly due to the need to remove the filter from the cigarette to obtain a useful dose administration (Apana and Berridge 2010). Even so, many excellent dose administrations were obtained which the subjects reported to have been representative of their normal smoking inhalations and which resulted in a subjective report of typical hedonic effects of smoking. A report of hedonic effects indicated a successful PET scan, while lack of it indicated failure to achieve sufficient dose administration to acquire an image. Therefore, we did not otherwise attempt to analyze correlation of subjective effects in data analysis, especially as the administration was limited to a single puff.

Brain scans were successfully obtained from nine subjects, in each subject's first successful PET scan procedure. The experimental design allowed an average of 4.4 half-lives of decay time between the first and second scans of a subject. This decreased radioactivity 20-fold in addition to the decline noted in the decay-corrected time-activity curves as shown (Figs. 2, 3, 4, 5, and 6). Therefore, residual radioactivity from the first administration was neglected during analysis of the lung and blood data from the second.

Data acquisition

Because of the difficulties described above, 13 interpretable scans were obtained from the 11 subjects who completed the study, out of 22 possible. Because of the intentional bias toward the brain scan, there were a total of nine usable brain scans and four lung scans. Similarly, six arterial and nine venous blood curves were obtained. Arterial data was not obtained in several subjects because of typical difficulties in arterial catheter placement, subject refusal, and catheter clotting during waiting periods despite use of heparin. The PET scan duration, initially 15 min, was reduced to 10 min when it became clear that this was sufficient to acquire the data. Subjects tolerated the time in the scanner easily.

The zero point of the rise time calculation was the nicotine concentration threshold of 20% of maximum value as described above. An earlier origin timepoint shown on accompanying figures is the time at which the puff from the cigarette was taken. The time between the puff (zero point) and the take-off point of a curve represents the time required for inhalation, for nicotine to enter the blood, and for blood to reach the wrist (blood curve) or the brain (brain curve). Because it was necessary to start the scanner as the command was given to inhale, there is a short additional lag (1–3 s) in the PET scan curves which is small in comparison to the 10-s time frame of the scanner data acquisition. This time period is

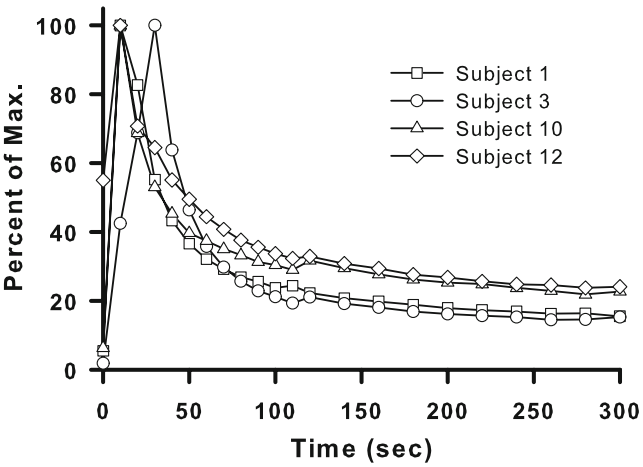

Fig. 2 Lung kinetics of inhaled [^{11}C]nicotine, all four successful lung scans. Normalized nicotine content in lung vs. time from time of puff. Subject no. 3 took two rapid consecutive puffs, which may have prolonged the rise on that trial

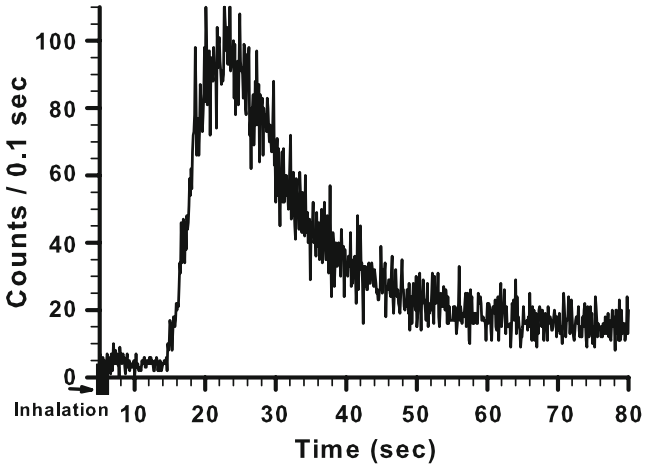

Fig. 3 Arterial blood curve, subject 6 brain scan, 0.1 s sampling, no damping. Time scale is 0 is the start of the puff

noted on the figures as an inhalation zone. However, we stress that the most important information reported here is the shape of the curves in brain and blood, and the rise time required for nicotine to change from low to high levels in the brain. A rate of rise would refer to an average slope of the rising portion of the concentration curve. The rise time is closely related to that slope as the time required for each curve to rise from 20% to 80% of its own maximum. While not being strictly independent from such events as the puff onset, this quantity does not refer to any external event and is measured directly from the shape of each curve independent of the zero point of the time axis. Another way to think of this reported rise time would be as the time required for the nicotine concentration to achieve its central 60% of rise in value. It can easily be expressed as a rate in units of percent of maximum per second, calculated as 60 divided by the rise time.

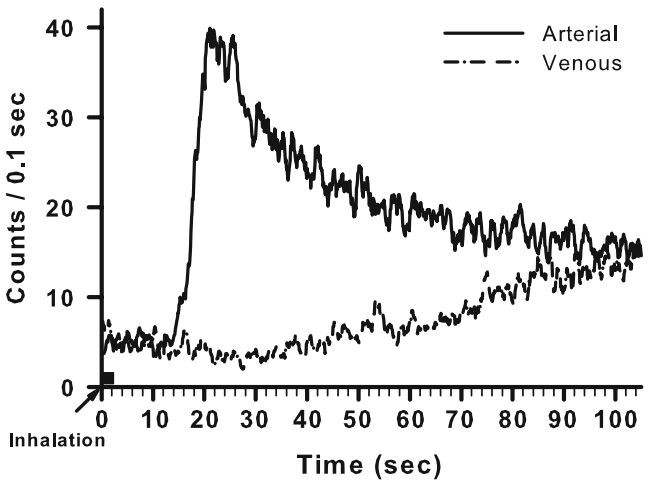

Fig. 4 Paired arterial and venous blood curves, subject 7 brain scan, 0.1 s sampling but with 1 s damping for clarity. Time scale is from the time of the start of the puff for both curves

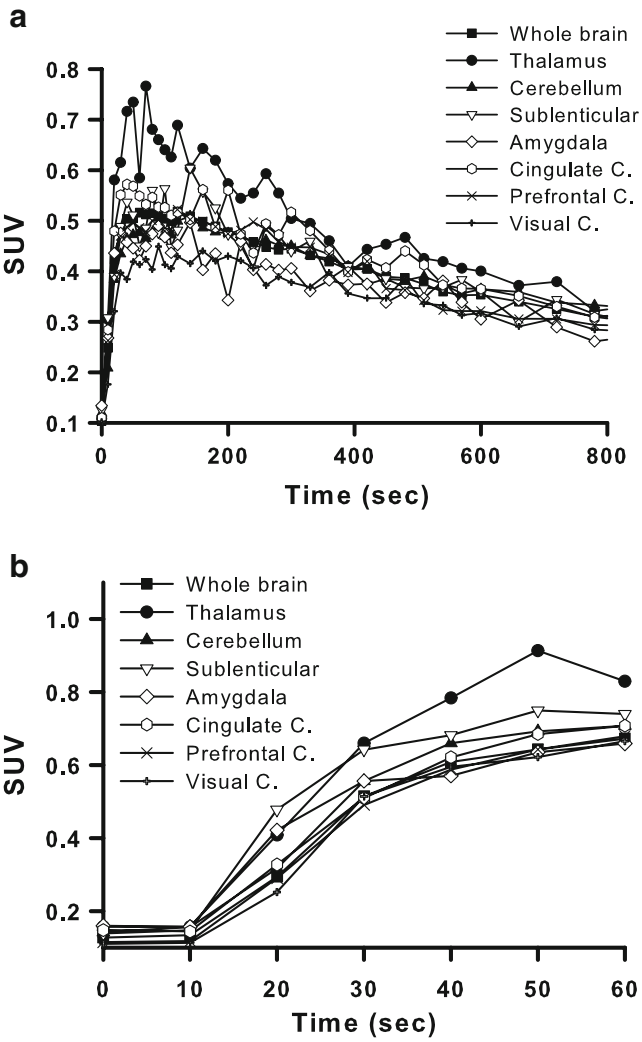

Fig. 5 **a** Regional brain curves (subject 3) over 13 min, SUV values vs. time in seconds from the start of the inhaled puff. *SUV* = standard uptake value (unitless fractional dose uptake per fractional body mass). **b** Expanded time scale showing rising portions of regional brain curves (subject 10)

Similarly, the absolute magnitude of any curve was mainly dependent upon the [^{11}C]nicotine dose deposited on the cigarette and the efficiency with which the subject inhaled it. Again, the primary interest is in the shape of the curve. It is not our intent, and indeed with this experimental design it is not possible, to measure the magnitude of nicotine administration from smoking a typical cigarette. Most of the data is therefore normalized or is shown in convenient units which are not highly relevant to our conclusions.

Lung uptake

Lung scans were uniform with the appearance of typical healthy lung ventilation images. Image photographs are not shown here because they were unremarkable, uniform with

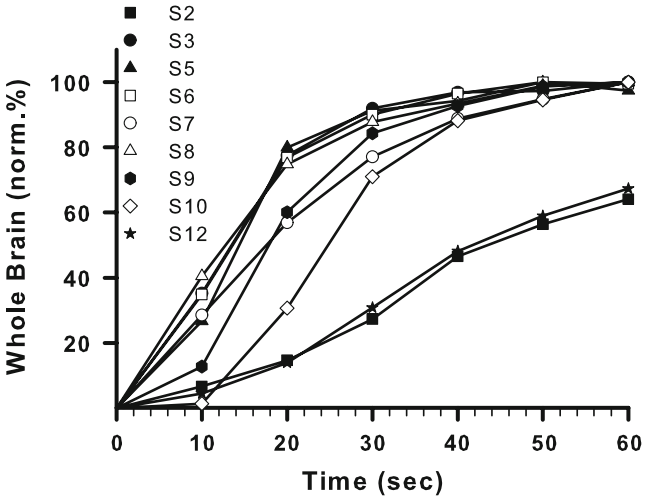

Fig. 6 Whole brain uptake curves from all subjects with time scale shortened to show rise time detail

no notable regional distribution features. Nicotine vapor was not trapped on the mucosa by ion exchange or any other mechanisms but was distributed through the lung in the same way as any neutral gas. The kinetic data (Fig. 2) showed that delivery to the lung was fast with respect to the 10-s scan frames as might be expected, followed by rapid washout into the blood. Lung uptake kinetics is therefore more accurately estimated from the arterial blood curve, when available, as an upper limit for the time of delivery and absorption from the lung. All acquired curves are shown. Very fast uptake was noted except in subject 3. Curves rose from baseline to maximum in less than one 10-s scan frame. Subject 12 inhaled across the transition between the first two frames, resulting in an artifactual appearance of a scan start above baseline and a two-frame uptake. Only the uptake in subject 3 was prolonged (20–30 s). Subject 3 had difficulty in taking the first puff and, contrary to instructions, drew an initial short and shallow inhalation followed by a second inhalation. All curves show rapid washout which appears to be biphasic, with a long-term component. The short component appears to be less than, but near, 20 s. Perhaps the most important observation is that absorption is essentially complete in 40–60 s.

Blood curves

Smoked nicotine moves into the arterial blood from the lung. A typical arterial blood curve is shown (Fig. 3). The figure was chosen for its representative shape and relatively high total uptake for clarity. All arterial curves were remarkably similar in shape. The rapid sampling (10 Hz) resulted in a high noise level and fine time resolution. The nicotine bolus arrived at the arterial sampling site at approximately 10–15 s after the start of inhalation. This was later than arrival in the brain (at approximately 5 s) because the sampling point at the wrist is more distal in the circulation than the brain. The rise times of the arterial curves (from 20% to 80% of the maximum value) were consistent with the fast observed lung kinetics. Arterial rise times were 3.6–4.5 s (average, 4.0 s, $n=6$), and widths were about 8–12 s, although the judgment was subjective due to "tailing" of the peaks. Rapid rise was followed by a relatively extended maximum and then a slower decline with a half time of approximately 10 s. Within 40 s of onset, the entire bolus was finished.

In contrast, venous blood activity rose gradually if at all during the observation period to attain only very low values. Many venous curves were only noisy baselines, showing no rise in activity over background through the entire data collection time (10 min). The curve that showed the largest venous increase is shown (Fig. 4) paired with the arterial curve obtained during the same scan. A 1-s damping factor was applied to both curves to reduce noise for this figure. It should be noted that in comparison with prior literature, these venous concentration data are truncated to a short observation time. The extended washout of nicotine from the brain would be expected, eventually, to result in higher venous concentrations. Data reported here relate only to the initial minutes following a single inhalation.

Brain uptake

No averaging of raw data was done due to the variation in the timing between start of data collection and the inhalation and to variable magnitude of the inhaled doses of radioactivity. Thus, all accompanying figures show individual data. As mentioned above, the rise time was calculated as the time during which, in each subject's brain, the nicotine concentration rose from 20% to 80% of its maximum value. Brain uptake consisted of an initial rise after which variations, due to imaging statistics, became evident. The concentration then generally continued to rise at a slower rate. It reached a maximum within 1 min and then declined as nicotine washed out of the tissue. The use of the 20% and 80% levels minimized potential variations arising from image noise and from the lingering rise, while providing an objective measure of the time required for the majority of the radioactivity to arrive in the brain.

Nicotine arrived in the brain beginning approximately 5 s after start of inhalation, and then was retained with a half time longer than 15 min. The nicotine uptake in the different brain regions that were studied (Fig. 5a, b) was remarkably uniform in comparison to some neuroreceptor-binding radiotracers. Tracers that bind with high affinity to receptors can accumulate in receptor-rich regions in at least several-fold higher amounts than in receptor-poor regions, but that is not the case here. Data from regions rich in

nicotinic acetylcholine receptors (prefrontal cortex, thalamus, anterior cingulate cortex, and sublenticular region) consistently appeared to take up more nicotine than other regions, but only by small amounts. The thalamus, for example, appeared as the region of highest uptake in each brain scan, while the visual cortex was at the lower edge of the cluster of regional curves from each subject, yet the differences were not necessarily significant. Curves from different regions from a single subject were similar in shape and magnitude regardless of receptor content and, when graphed together, tightly clustered around the whole-brain values. This result is consistent with our prior result during testing of [^{11}C]nicotine for receptor measurement (Muzic et al. 1998). In that work, it was found that receptor binding was only a marginally detectable feature of regional nicotine kinetics. This was part of our rationale for use of racemic rather than optically pure nicotine. In particular, the rise time between 20% and 80% of the maximum value was the same regardless of brain region. Therefore, for determination of rise time and for comparison among subjects, only the whole-brain regional data was used (Fig. 6). Those calculated rise times are shown in Table 1. Nicotine rise times were as quick as 11 s in the most rapid-to-rise subject and 69 s in the slowest. The rise times appeared to cluster into three groups (N=9). Six of nine subjects fell into a "short" rise time range, rising in 11–16 s, average 13±2 s. One subject had an "intermediate" rise time of 24, and two subjects had "long" rise times of 68 and 69 s (Table 1).

Discussion

Arterial blood levels of nicotine rose rapidly to achieve maximum concentrations within 4 s of the single puff (Fig. 3). The arterial and venous blood curves are consistent with rapid placement of the drug into the arterial circulation by pulmonary administration, and with high first-pass extraction and retention of nicotine in most tissues (Muzic et al. 1998). Recirculation of nicotine was negligible during the first 60–120 s, as shown by low concentration in the venous blood. The shape of the arterial curve (Fig. 3) was therefore due only to absorption from the lung. It was consistent with previously reported data (Rose et al. 1999). Further, it is not excluded that some blood curve data, especially for venous blood, might be due to background radiation artifacts from dose in the subject's body, in spite of efforts to effectively shield the detector. The curves shown were chosen partly because they contained this feature as well as the features of the arterial bolus that were seen in all of the blood data. Some arterial curves, however, returned close to the initial baseline level after the bolus, and some venous blood curves appeared completely flat throughout the study. If the blood curve shown is integrated (Fig. 7), features of the integral such as the initial rise time are consistent with the brain uptake data. This is expected from high first-pass extraction and retention. The figure shows that [^{11}C]nicotine apparently acts as a reasonably good perfusion tracer. The continued rise may be due to the background radiation artifact mentioned above. Nicotine washout from the brain, visible in Fig. 5a, did not produce a corresponding rise in activity in the venous blood. It is therefore likely that nicotine was efficiently extracted and metabolized by organs other than the brain, thereby keeping the venous blood concentration low (Halldin et al. 1992; Muzic et al. 1998; Nordberg et al. 1995).

Brain rate-of-rise In the "Materials and methods" section, we defined two different temporal quantities. The first quantity we refer to as the "lag," "latency," or the "lag-to-rise." This is the delay between the moment of cigarette puff when the drug is administered and the moment that a

Table 1 Observed rise times in the brain of each subject in ascending order of rise time

Subject number	Cigarettes/day	Rise time (s)
10	35	11
8	4	11
7	10	12
5	10	13
9	10	15
3	20	16
6	10	24
2	40	68
12	20	69

Subject study ID numbers and self-reported smoking rate are also shown

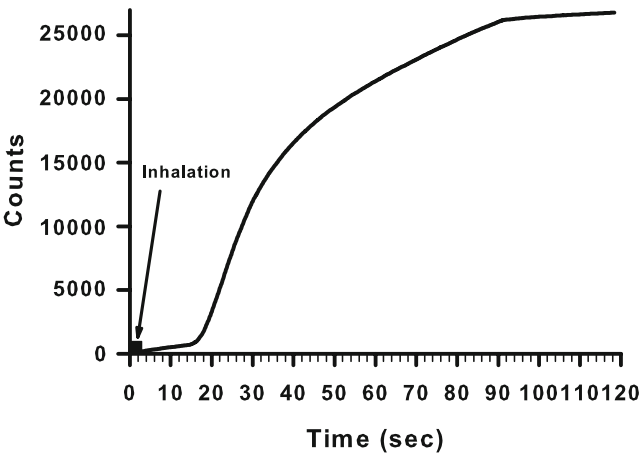

Fig. 7 Integrated arterial blood curve, subject 6

rise in drug concentration can be detected in the brain. The second quantity, related to the slope of the rising portion of the tissue curve, is the "rise time" or the time duration between the beginning of the rise of tissue concentration (defined here as the moment of 20% of maximal concentration) and the moment when the brain concentration levels approach their eventual maximum (defined here as the moment of 80% maximal concentration). It is this second, rise time, value that is related to the concept of *rate*-of-rise. Of these two quantities, both will influence the time required for peak concentration to be reached, but the rise time is likely to be most relevant to the actual impact of the drug on neurobiological and psychological effects that have been reported by others to depend on rate-of-rise. That is because the rise time (slope of the rising portion of the tissue curve) best captures the timing of the transition from low to high levels of drug in the brain that is most directly related to impact.

Here, the lag-to-rise, from the behavioral puff to the beginning of a concentration increase in the brain, was approximately 5 s, though the temporal resolution of the PET scan limits the precision of that estimate. Perhaps more importantly, the rise times in brain (Table 1) clustered around 13 s for 66% of subjects, while measured values for the other subjects were between 24 and 70 s.

Rise times from individual regions of interest were the same as whole brain for each subject, within the limits of the statistical data variability in the smaller PET scan regions (Fig. 5b), and curve shapes of all regions were similar. Apparent differences in regional uptake curves (thalamus vs. visual cortex, for example) should be interpreted with care because the data were not corrected for perfusion differences. The result shows, as expected, that nicotine distribution is consistent with prior results showing a minor effect of specific receptor binding on nicotine kinetics (Muzic et al. 1998) and verifies that the use of racemic tracer to measure uptake was justified. Because of the consistent rates of rise and the better image statistics provided by the whole brain region of interest, only data from the whole brain region are further considered here.

The first conclusion that may be drawn is that a single puff from a cigarette produces a rise time for nicotine in the brain that is faster than 15 s for most subjects. The second conclusion is that individual differences can cause this rise time to be longer for some subjects. However, the smoker's experience, or rate of smoking expressed as smoked cigarettes per day, did not appear to be correlated with the rise time (Table 1). No other possible cause of the longer rise times in three subjects is apparent from the available data. Causes of variability will require further study. For now, we can only speculate that individual differences in rise time may be due to variable aspects of smoking a cigarette (puff efficiency, inspiration rate, inspiratory volume, coughing, etc.). These may correlate with details of the individual's experience, degree of habituation to cigarettes, or physiology.

An issue that we sought to address was whether smoking can deliver nicotine to the brain sufficiently rapidly that this may contribute to its addiction liability. Our results indicate that the rate of rise of nicotine in the brain after smoking is indeed fast enough to recruit potential mechanisms related to drug impact and addiction that have been described in the literature for nicotine and for other drugs of abuse (Samaha and Robinson 2005 for review). For example, the most common (13 s) rise time for nicotine concentration in the brain observed in this study was similar to, and possibly even faster than, the rapid rise reported in human brain for smoked cocaine (Volkow et al. 1995, 1996a). Although cocaine and nicotine are very different drugs, varying the rate at which they reach the brain has some common effects. For example, both nicotine and cocaine are more effective in inducing psychomotor sensitization when administered intravenously over 5 s than when administered over 25–100 s (Samaha et al. 2004, 2005; Samaha and Robinson 2005). Furthermore, when delivered rapidly, both nicotine and cocaine are also more effective in inducing immediate early genes in brain regions such as the prefrontal cortex and dorsal and ventral striatum. The ability of drugs to induce immediate early genes is thought to represent the first step in a cascade of intracellular events thought to contribute to drug-induced forms of plasticity that may contribute to addiction (Hyman et al. 2006; Maze et al. 2010). In addition, for cocaine, the variation in the speed of intravenous delivery between 10 and 60 s influences its hedonic effects (Abreu et al. 2001; Nelson et al. 2006), and similar effects have been described for other drugs (de Wit et al. 1992; Ferrario et al. 2008), which could also influence the propensity to continue use. Finally, it was recently reported that when given extended access to cocaine, rats dramatically increased the amount they self-administered if each injection was delivered over 5–45 s, but not when each injection was administered over 90 s (Wakabayashi et al. 2009). Importantly, variation in the speed of i.v. cocaine delivery over this range has no effect on the ability of cocaine to increase dopamine overflow in the striatum as assessed with microdialysis (Ferrario et al. 2008).

The comparisons between the rise time in the present work and the physiological and psychological effects upon rodents and humans of the injected bolus duration in other reports are instructive. However, it must also be noted that there is a difference between the *duration of a bolus infusion* into venous blood and the *actual duration of the drug concentration rise* produced in the brain tissue as that bolus reaches the brain. Most literature data relies upon measurement of the duration of i.v. bolus infusions. There

is a spreading effect on an injected bolus as it travels through the circulation that is proportional to the distance traveled through veins and arteries (Nelson et al. 1990). Also following an intravenous injection, the bolus is subjected to additional mixing as it flows through the beating right heart to the lung, and so both the lag-to-rise and the rise time in the brain are increased further. To compare actual human data regarding intravenous injection and smoked administration of nicotine, we refer to our previous work (Muzic et al. 1998) using a <3-s intravenous bolus of [^{11}C]nicotine. For comparison, a brain curve from that work is shown in Fig. 8 co-plotted with a brain curve generated by smoking administration in this study. Intravenous administration required at least 75 s lag time from injection (>125 s in the curve shown) to complete the majority of the rise in brain nicotine concentration, as compared to approximately 30 s here after smoking administration. More importantly, the rise time once the nicotine began to arrive in the brain tissue was more than three times longer (>48 s, 66 s in the curve shown) after the 3 s. i.v. infusion, compared to smoking administration (<16 s). While more must be done in order to compare dose–response effects, it seems reasonable to suggest that smoking produces a much faster rate of rise in the human brain than i.v. injection. Further, such spreading of an i.v. bolus is likely to be seen regardless of the substance being administered (Nelson et al. 1990). This observation may in itself be useful for the interpretation of i.v. injection studies. Though bolus spreading in rodents has not been measured, if a 3-s i.v. bolus in a human spreads to a 48-s brain rise time, it is reasonable that a 5-s i.v. bolus in a rat, which has been shown to have a strong rate-of-rise effect, might spread to a rise time in brain of at least 13 s, which is the rise time in human brain observed here.

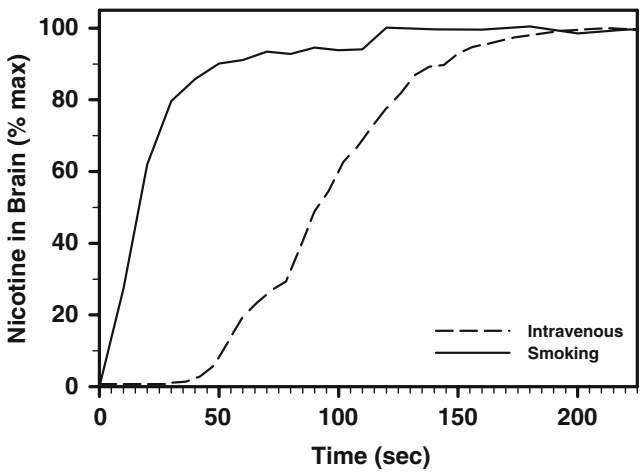

Fig. 8 Brain curves from i.v. administration (from underlying data of Muzic et al. 1998) and smoked administration (S9). Curves are interpolated, smoothed, and normalized to maximum uptake. Time zero is start of inhalation (smoking) or start of 3 s infusion (i.v.)

All considerations above, taken together, suggest that the rise times we observed in the brain after smoking are not slower, and may be faster, than those resulting from infusion durations that were found to influence euphoria and other subjective effects in humans and influence susceptibility to sensitization in rodents. The rise time of smoked nicotine in the human brain therefore could have strong effects upon factors potentially relevant to addiction, including hedonic impact, tolerance, and mesolimbic sensitization. However, our observation of some considerably longer rise times in a minority of subjects indicates that at least some smokers may experience cerebral nicotine kinetics that take longer to rise. Details of a smoker's inhalation technique affecting the rate and effectiveness of their "puff" or details of nicotine release by cigarettes and tobacco (Apana and Berridge 2010; Gourlay and Benowitz 1997; Henningfield et al. 2000; Henningfield and Keenan 1993; Rose et al. 1999, 2007; Stitzer and de Wit 1998) may affect the bolus rise times and their effects on addiction. Some smokers may have inhalation characteristics that could conceivably reduce the impact of the rate of rise of nicotine in the brain in ways that might be relevant to their susceptibility to addiction, though our observations do not permit conclusions related to any cause of the observed variations. Finally, we note again that the measurements presented here are the result of single-bolus inhalation. A smoker typically inhales about 15 times from a cigarette at intervals of about 20 s, with wide variability. Therefore, the actual brain curve of nicotine in a smoker consists of a convolution of the brain curve shown in Figs. 5 and 6 over the puffing pattern used by the smoker. This essentially produces a step function formed from our measured curve adjusted for the smoker's inhalation (Rose et al. 1999) and then repeated and added approximately 15 times at intervals determined by the smoker, which may prolong the effective rise time. However, smokers report immediate hedonic effects (a "rush") from their first single puff on a cigarette. The relevance of a sequence of puffs versus a single puff deserves exploration in future studies. Also of interest for future work would be the exploration of possible correlation of rise time with physiologic, autonomic, and behavioral measures of nicotine effects and with measures of smoking dependence.

Conclusion

The rapid rise time of nicotine in human brain that we have observed after a single smoked puff was comparable to the rise time reported for a single puff of cocaine in the brains of cocaine addicts and comparable also to rise times reported to lead to maximal impacts of nicotine and other drugs. Therefore, we expect that a rapid rate of rise of nicotine in

the brain can be considered as a potential contributing factor to addiction of some smokers to nicotine.

Acknowledgments We deeply appreciate the insight and assistance of Dr. Kent Berridge of the University of Michigan with data interpretation and for valuable comments and suggestions to improve the manuscript. We are also indebted to Dr. Terry Robinson of the University of Michigan for helpful critical reading of the manuscript and useful discussions. Constructive comments by the Editor and reviewers have also significantly contributed to the quality of this manuscript. We thank Dr. Joanna Fowler of Brookhaven National Laboratory for valuable discussions and encouragement. Apparatus design and construction and cyclotron operation by Mr. Ken Volker, and PET scanning assistance provided by Mr. Ron Rogan and Ms. Ellie Leedom are gratefully acknowledged. This work was supported by the Philip Morris External Research Program; Philip Morris USA, Inc., and performed at a previous address of 3D Imaging, in collaboration with Case Western Reserve University, Cleveland, OH, USA.

References

Abreu ME, Bigelow GE, Fleisher L, Walsh SL (2001) Effect of intravenous injection speed on responses to cocaine and hydromorphone in humans. Psychopharmacology (Berl) 154:76–84

Apana SM, Berridge MS (2010) Cigarettes labeled with [^{11}C]nicotine: formulation and administration for PET inhalation. J Labelled Compd Radiopharm 53:6–10

Bergstrom M, Nordberg A, Lunell E, Antoni G, Langstrom B (1995) Regional deposition of inhaled 11C-nicotine vapor in the human airway as visualized by positron emission tomography. Clin Pharmacol Ther 57:309–317

Berridge MS, Heald DL, Muswick GJ, Leisure GP, Voelker KW, Miraldi F (1998) Biodistribution and kinetics of nasal carbon-11-triamcinolone acetonide. J Nucl Med 39:1972–1977

Berridge MS, Lee Z, Heald DL (2000) Pulmonary distribution and kinetics of inhaled [11C]triamcinolone acetonide. J Nucl Med 41:1603–1611

Berridge MS, Heald DL, Lee Z (2003) Imaging studies of biodistribution and kinetics in drug development. Drug Dev Res 59:208–226

Brown PL, Kiyatkin EA (2005) Brain temperature change and movement activation induced by intravenous cocaine delivered at various injection speeds in rats. Psychopharmacology (Berl) 181:299–308

Cleton A, Mazee D, Voskuyl RA, Danhof M (1999) Rate of change of blood concentrations is a major determinant of the pharmacodynamics of midazolam in rats. Br J Pharmacol 127:227–235

Comer SD, Collins ED, MacArthur RB, Fischman MW (1999) Comparison of intravenous and intranasal heroin self-administration by morphine-maintained humans. Psychopharmacology (Berl) 143:327–338

Cone EJ (1995) Pharmacokinetics and pharmacodynamics of cocaine. J Anal Toxicol 19:459–478

de Wit H, Bodker B, Ambre J (1992) Rate of increase of plasma drug level influences subjective response in humans. Psychopharmacology (Berl) 107:352–358

de Wit H, Dudish S, Ambre J (1993) Subjective and behavioral effects of diazepam depend on its rate of onset. Psychopharmacology (Berl) 112:324–330

Evans SM, Cone EJ, Henningfield JE (1996) Arterial and venous cocaine plasma concentrations in humans: relationship to route of administration, cardiovascular effects and subjective effects. J Pharmacol Exp Ther 279:1345–1356

Ferrario CR, Shou M, Samaha AN, Watson CJ, Kennedy RT, Robinson TE (2008) The rate of intravenous cocaine administration alters c-fos mRNA expression and the temporal dynamics of dopamine, but not glutamate, overflow in the striatum. Brain Res 1209:151–156

Gatley SJ, Volkow ND, Fowler JS, Dewey SL, Logan J (1995) Sensitivity of striatal [11C]cocaine binding to decreases in synaptic dopamine. Synapse 20:137–144

Gatley SJ, Volkow ND, Gifford AN, Ding YS, Logan J, Wang GJ (1997) Model for estimating dopamine transporter occupancy and subsequent increases in synaptic dopamine using positron emission tomography and carbon-11-labeled cocaine. Biochem Pharmacol 53:43–52

Gorelick DA (1998) The rate hypothesis and agonist substitution approaches to cocaine abuse treatment. Adv Pharmacol 42:995–997

Gourlay SG, Benowitz NL (1997) Arteriovenous differences in plasma concentration of nicotine and catecholamines and related cardiovascular effects after smoking, nicotine nasal spray, and intravenous nicotine. Clin Pharmacol Ther 62:453–463

Halldin C, Nagren K, Swahn CG, Langstrom B, Nybäck H (1992) (S)- and (R)-[^{11}C]nicotine and the metabolite (R/S)-[^{11}C]cotinine. Preparation, metabolite studies and in vivo distribution in the human brain using PET. Int J Rad Appl Instrum [B] 19:871–880

Hatsukami DK, Fischman MW (1996) Crack cocaine and cocaine hydrochloride. Are the differences myth or reality? JAMA 276:1580–1588

Henningfield JE, Keenan RM (1993) Nicotine delivery kinetics and abuse liability. J Consult Clin Psychol 61:743–750

Henningfield JE, Stapleton JM, Benowitz NL, Grayson RF, London ED (1993) Higher levels of nicotine in arterial than in venous blood after cigarette smoking. Drug Alcohol Depend 33:23–29

Henningfield JE, Fant RV, Gitchell J, Shiffman S (2000) Tobacco dependence. Global public health potential for new medications development and indications. Ann N Y Acad Sci 909:247–256

Hyman SE, Malenka RC, Nestler EJ (2006) Neural mechanisms of addiction: the role of reward-related learning and memory. Annu Rev Neurosci 29:565–598

Kollins SH, Rush CR, Pazzaglia PJ, Ali JA (1998) Comparison of acute behavioral effects of sustained-release and immediate-release methylphenidate. Exp Clin Psychopharmacol 6:367–374

Lee Z, Berridge MS (2002) PET imaging-based evaluation of aerosol drugs and their delivery devices: nasal and pulmonary studies. IEEE Trans Med Imaging 21:1324–1331

Lee Z, Berridge MS, Finlay WH, Heald DL (2000) Mapping PET-measured triamcinolone acetonide (TAA) aerosol distribution into deposition by airway generation. Int J Pharm 199:7–16

Lee Z, Ljungberg M, Muzic RF Jr, Berridge MS (2001) Usefulness and pitfalls of planar gamma-scintigraphy for measuring aerosol deposition in the lungs: a Monte Carlo investigation. J Nucl Med 42:1077–1083

Lunell E, Bergstrom M, Antoni G, Langstrom B, Nordberg A (1996) Nicotine deposition and body distribution from a nicotine inhaler and a cigarette studied with positron emission tomography. Clin Pharmacol Ther 59:593–594

Marsch LA, Bickel WK, Badger GJ, Rathmell JP, Swedberg MD, Jonzon B, Norsten-Hoog C (2001) Effects of infusion rate of intravenously administered morphine on physiological, psychomotor, and self-reported measures in humans. J Pharmacol Exp Ther 299:1056–1065

Maze I, Covington HE III, Dietz DM, LaPlant Q, Renthal W, Russo SJ, Mechanic M, Mouzon E, Neve RL, Haggarty SJ, Ren Y, Sampath SC, Hurd YL, Greengard P, Tarakhovsky A, Schaefer A, Nestler EJ (2010) Essential role of the histone methyltransferase G9a in cocaine-induced plasticity. Science 327:213–216

Muzic RF Jr, Nelson AD, Miraldi F (1997) Monitoring the arterial radioactivity input function. In: Leondes CT (ed) Medical

imaging techniques and applications, vol 4, General Anatomy. Gordon and Breach Science Publishers, Amsterdam, pp 85–145
Muzic RF Jr, Berridge MS, Friedland RP, Zhu N, Nelson AD (1998) PET quantification of specific binding of carbon-11-nicotine in human brain. J Nucl Med 39:2048–2054
Nelson AD, Muzic RF Jr, Miraldi F, Muswick GJ, Leisure GP, Voelker W (1990) Continuous arterial positron monitor for quantitation in PET imaging. Am J Physiol Imaging 5:84–88
Nelson RA, Boyd SJ, Ziegelstein RC, Herning R, Cadet JL, Henningfield JE, Schuster CR, Contoreggi C, Gorelick DA (2006) Effect of rate of administration on subjective and physiological effects of intravenous cocaine in humans. Drug Alcohol Depend 82:19–24
Nordberg A, Hartvig P, Lundqvist H, Antoni G, Ulin J, Langstrom B (1989) Uptake and regional distribution of (+)-(R)- and (-)-(S)-N-[methyl-^{11}C]- nicotine in the brains of rhesus monkey. An attempt to study nicotinic receptors in vivo. J Neural Transm Park Dis Dement Sect 1:195–205
Nordberg A, Hartvig P, Lilja A, Viitanen M, Amberla K, Lundqvist H, Andersson Y, Ulin J, Winblad B, Langstrom B (1990) Decreased uptake and binding of ^{11}C-nicotine in brain of Alzheimer patients as visualized by positron emission tomography. J Neural Transm Park Dis Dement Sect 2:215–224
Nordberg A, Lundqvist H, Hartvig P, Lilja A, Langstrom B (1995) Kinetic analysis of regional (S)(-)11C-nicotine binding in normal and Alzheimer brains–in vivo assessment using positron emission tomography. Alzheimer Dis Assoc Disord 9:21–27
Nybäck H, Halldin C, Ahlin A, Curvall M, Eriksson L (1994) PET studies of the uptake of (S)- and (R)-[^{11}C]nicotine in the human brain: difficulties in visualizing specific receptor binding in vivo. Psychopharmacology (Berl) 115:31–36
Resnick RB, Kestenbaum RS, Schwartz LK (1977) Acute systemic effects of cocaine in man: a controlled study by intranasal and intravenous routes. Science 195:696–698
Rose JE, Behm FM, Westman EC, Coleman RE (1999) Arterial nicotine kinetics during cigarette smoking and intravenous nicotine administration: implications for addiction. Drug Alcohol Depend 56:99–107
Rose JE, Behm FM, Salley AN, Bates JE, Coleman RE, Hawk TC, Turkington TG (2007) Regional brain activity correlates of nicotine dependence. Neuropsychopharmacology 32:2441–2452
Samaha AN, Robinson TE (2005) Why does the rapid delivery of drugs to the brain promote addiction? Trends Pharmacol Sci 26:82–87
Samaha AN, Mallet N, Ferguson SM, Gonon F, Robinson TE (2004) The rate of cocaine administration alters gene regulation and behavioral plasticity: implications for addiction. J Neurosci 24:6362–6370
Samaha AN, Yau WYW, Yang P, Robinson TE (2005) Rapid delivery of nicotine promotes behavioral sensitization and alters its neurobiological impact. Biol Psych 57:351–360
Samaha AN, Reckless GE, Seeman P, Diwan M, Nobrega JN, Kapur S (2008) Less is more: antipsychotic drug effects are greater with transient rather than continuous delivery. Biol Psychiatry 64:145–152
Schneider NG, Lunell E, Olmstead RE, Fagerstrom KO (1996) Clinical pharmacokinetics of nasal nicotine delivery. A review and comparison to other nicotine systems. Clin Pharmacokinet 31:65–80
Spencer TJ, Biederman J, Ciccone PE, Madras BK, Dougherty DD, Bonab AA, Livni E, Parasrampuria DA, Fischman AJ (2006) PET study examining pharmacokinetics, detection and likeability, and dopamine transporter receptor occupancy of short- and long-acting oral methylphenidate. Am J Psychiatry 163:387–395
Stitzer ML, de Wit H (1998) Abuse liability of nicotine. In: Benowitz NL (ed) Nicotine safety and toxicity. Oxford University Press, London, pp 147–157
Ungerstedt U, Arbuthnott GW (1970) Quantitative recording of rotational behavior in rats after 6-hydroxy-dopamine lesions of the nigrostriatal dopamine system. Brain Res 24:485–493
Volkow ND, Fowler JS, Wolf AP, Schlyer D, Shiue CY, Alpert R, Dewey SL, Logan J, Bendriem B, Christman D (1990) Effects of chronic cocaine abuse on postsynaptic dopamine receptors. Am J Psychiatry 147:719–724
Volkow ND, Wang GJ, Fowler JS, Logan J, Schlyer D, Hitzemann R, Lieberman J, Angrist B, Pappas N, MacGregor R (1994) Imaging endogenous dopamine competition with [11C]raclopride in the human brain. Synapse 16:255–262
Volkow ND, Ding YS, Fowler JS, Wang GJ, Logan J, Gatley JS, Dewey S, Ashby C, Liebermann J, Hitzemann R, Wolf AP (1995) Is methylphenidate like cocaine? Studies on their pharmacokinetics and distribution in the human brain. Arch Gen Psychiatry 52:456–463
Volkow ND, Ding YS, Fowler JS, Wang GJ (1996a) Cocaine addiction: hypothesis derived from imaging studies with PET. J Addict Dis 15:55–71
Volkow ND, Gatley SJ, Fowler JS, Logan J, Fischman M, Gifford AN, Pappas N, King P, Vitkun S, Ding YS, Wang GJ (1996b) Cocaine doses equivalent to those abused by humans occupy most of the dopamine transporters. Synapse 24:399–402
Volkow ND, Wang GJ, Fowler JS, Logan J, Angrist B, Hitzemann R, Lieberman J, Pappas N (1997) Effects of methylphenidate on regional brain glucose metabolism in humans: relationship to dopamine D2 receptors. Am J Psychiatry 154:50–55
Volkow ND, Wang GJ, Fowler JS, Fischman M, Foltin R, Abumrad NN, Gatley SJ, Logan J, Wong C, Gifford A, Ding YS, Hitzemann R, Pappas N (1999) Methylphenidate and cocaine have a similar in vivo potency to block dopamine transporters in the human brain. Life Sci 65:L7–L12
Wakabayashi KT, Weiss MJ, Robinson TE (2009) Extended access to self-administered cocaine promotes a marked increase in drug intake if it is delivered rapidly (5-45s), but not slowly (90s). Soc Neurosci Abstr 159:P8
Wakasa Y, Takada K, Yanagita T (1995) Reinforcing effect as a function of infusion speed in intravenous self-administration of nicotine in rhesus monkeys. Nihon Shinkei Seishin Yakurigaku Zasshi 15:53–59