Eur J Nucl Med Mol Imaging (2008) 35:1692–1698
DOI 10.1007/s00259-008-0795-0

ORIGINAL ARTICLE

# SPECT imaging of $D_2$ dopamine receptors and endogenous dopamine release in mice

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Received: 9 January 2008 / Accepted: 25 March 2008 / Published online: 19 April 2008


**Abstract**
*Purpose* The dopamine $D_2$ receptor (D2R) is important in the mediation of addiction. [$^{123}$I]iodobenzamide (IBZM), a SPECT ligand for the D2R, has been used for in vivo studies of D2R availability in humans, monkeys, and rats. Although mouse models are important in the study of addiction, [$^{123}$I]IBZM has not been used in mice SPECT studies. This study evaluates the use of [$^{123}$I]IBZM for measuring D2R availability in mice.
*Methods* Pharmacokinetics of [$^{123}$I]IBZM in mice were studied with pinhole SPECT imaging after intravenous (i.v.) injection of [$^{123}$I]IBZM (20, 40, and 70 MBq). In addition, the ability to measure the release of endogenous dopamine after amphetamine administration with [$^{123}$I]IBZM SPECT was investigated. Thirdly, i.v. administration, the standard route of administration, and intraperitoneal (i.p.) administration of [$^{123}$I]IBZM were compared.
*Results* Specific binding of [$^{123}$I]IBZM within the mouse striatum could be clearly visualized with SPECT. Peak specific striatal binding ratios were reached around 90 min post-injection. After amphetamine administration, the specific binding ratios of [$^{123}$I]IBZM decreased significantly (−27.2%; $n$=6; $p$=0.046). Intravenous administration of [$^{123}$I]IBZM led to significantly higher specific binding than i.p. administration of the same dose. However, we found that i.v. administration of a dose of 70 MBq [$^{123}$I]IBZM might result in acute ethanol intoxication because ethanol is used as a preparative aid for the routine production of [$^{123}$I]IBZM.
*Conclusions* Imaging of D2R availability and endogenous dopamine release in mice is feasible using [$^{123}$I]IBZM single pinhole SPECT. Using commercially produced [$^{123}$I]IBZM, a dose of 40 MBq injected i.v. can be recommended.

**Keywords** Single photon emission computed tomography · Dopamine receptors · Mice · Corpus striatum · Pharmacokinetics

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## Introduction

The dopamine system plays an important role in the mediation of drug addiction [1], and the availability of the dopamine $D_2$ receptor (D2R) appears to be important in the acquisition of cocaine self-administration in monkeys and rats [2–4]. [$^{123}$I]iodobenzamide (IBZM) is a SPECT ligand frequently used to study D2R availability in humans. It has also been used in a number of laboratory animals such as rhesus monkeys and rats [5, 6]. Although mouse models are important for the study of addiction, studies of the D2R in mice using [$^{123}$I]IBZM SPECT have not yet been performed. The present study is directed at evaluating the use

and the route of administration of [$^{123}$I]IBZM for pinhole SPECT imaging in mice. First, the dose and pharmacokinetics of [$^{123}$I]IBZM were determined. Second, the ability to measure displacement of [$^{123}$I]IBZM by amphetamine-induced dopamine release was assessed, and third, intravenous (i.v.) administration was directly compared to intraperitoneal (i.p.) administration. Although i.v. injection of [$^{123}$I]IBZM is a standardized and direct route of administration, i.p. injection may offer several advantages with respect to anesthesia duration, alcohol toxicity, and repeated administration for longitudinal studies.

## Materials and methods

### Animals

Ten-week-old male c57BL/6J mice (23–28 g) were obtained from Harlan (Horst, the Netherlands). Animals were maintained on a 12:12-h light/dark cycle with lights on at 6:00 a.m. Room temperature was kept at 21°C, and animals were permitted water and mouse chow ad libitum. All experimental procedures were approved by the Committee for Animal Care of the Academic Medical Center, Amsterdam, the Netherlands. During the entire scanning procedure, mice were anesthetized by i.p. injections of a mixture of ketamine (126 mg/kg body weight), medotomidine (200 μg/kg body weight), and diazepam (12 mg/kg body weight).

### Experiment 1: [$^{123}$I]IBZM dose and pharmacokinetics

The goal of this sub-study was to determine a feasible dose, as well as to study the pharmacokinetics of in vivo [$^{123}$I]IBZM administration in mice. Commercially produced [$^{123}$I]IBZM (GE Healthcare, Eindhoven, the Netherlands) with a specific activity of approximately 550 MBq/nmol and a radiochemical purity >97% was used in all experiments. For the production of [$^{123}$I]IBZM, ethanol is used as a preparative aid, resulting in a final concentration of 8% *v*/*v* ethanol. Different doses (70 MBq in 0.35 ml, 40 MBq in 0.2 ml, and 20 MBq in 0.1 ml) of [$^{123}$I]IBZM were injected in the tail vein: Two mice first received a dose of 70 MBq and 9 days later, a subsequent dose of 40 MBq; one mouse received a dose of 70 MBq and 7 days later, a dose of 20 MBq; one mouse received a dose of 20 MBq only. Measurements were performed during 12-min intervals for up to 2 h post-injection.

### Experiment 2: amphetamine-induced dopamine release

Nine mice received a dose of 40 MBq [$^{123}$I]IBZM i.v. to determine striatal binding ratios 90 min after injection. Approximately 7 days later, [$^{123}$I]IBZM administration was repeated. An injection of 2.5 mg/kg body weight amphetamine (obtained from Sigma-Aldrich as sulphate salt) was then given i.p. 30 min prior to [$^{123}$I]IBZM administration [7], and 90 min after [$^{123}$I]IBZM administration, striatal binding ratios were determined (acquisition time 36 min). Ex vivo measurements using a gamma counter were obtained immediately after the SPECT acquisition.

### Experiment 3: intraperitoneal versus intravenous injection of [$^{123}$I]IBZM

Nine mice were given i.v. and i.p. injections at least 7 days apart. The route of administration was alternated across animals. A dose of 40 MBq [$^{123}$I]IBZM was administered both i.v., as well as i.p. Measurements were performed during 12-min intervals for up to 2 h post-injection. Additionally, to test the feasibility of 70 MBq [$^{123}$I]IBZM injection i.p., this dose was administered to four mice, and binding measurements were started 90 min post-injection and continued for 36 min. For all 13 animals, ex vivo measurements using a gamma counter were obtained immediately after the SPECT acquisition.

### SPECT imaging

The single pinhole SPECT system used in the present study has been extensively described earlier [8]. Briefly, a cylinder with a diameter of 25 mm, designed for tight fitting of the mouse, is positioned directly and horizontally above the pinhole aperture. A mechanical support allows precise manual adjustment of the cylinder in two directions: the distance of the cylinder to the pinhole aperture, which equals the radius of rotation (ROR), and adjustment along the axis of the cylinder to select the field of view.

The pinhole collimator is connected to an ADAC ARC3000© scintillation camera and has a focal length of 320 mm and an opening angle of 64°. In this study, a 2-mm pinhole aperture was used (system sensitivity approximately 0.036 cps/kBq at an ROR of 25 mm; spatial resolution 2.6 mm FWHM [8]), and 50 projections of 12 s per projection were acquired for experiments 1 and 3 (for experiment 2, 50 projections of 30 s were acquired). All experiments were acquired, step and shoot, with a 20% energy window around 159 keV in a 64×64 matrix, ROR of 25 mm, and field of view of 31.5 mm. Reconstruction was performed using a HERMES© application program, utilizing filtered back projection and adapted to pinhole SPECT according to the conversion algorithm of Feldkamp [9]. The ramp filter was used as a reconstruction filter with a Butterworth post-reconstruction filter (10.2 cycles per centimeter, order 5). Images were reconstructed with a voxel size of 0.4×0.4×0.4 mm$^3$.

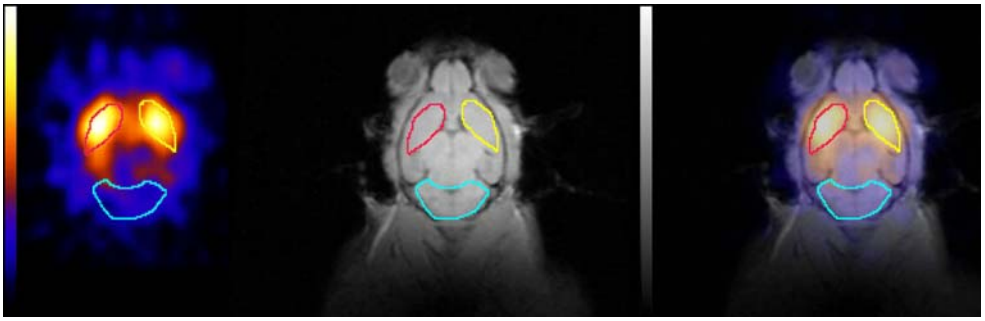

**Fig. 1** Sample slice from a [$^{123}$I]IBZM SPECT image of a mouse (*left*). ROIs for the striatum (*red* and *yellow*) and cerebellum (*blue*) were defined on a MR image of one mouse (*middle*). On the *right*, a fusion image of the MR and [$^{123}$I]IBZM SPECT image is shown

Regions of interest (ROIs) for the striatum and cerebellum were defined on a magnetic resonance (MR) image of one mouse as described previously [10]. The size of the striatal ROIs was 33 pixels on each side, and the size of the cerebellar ROI was 50 pixels. These ROIs were used as a template (Fig. 1). The template was positioned manually (without changing the size and form of the ROIs) on the SPECT images with the backing of anatomical information from the MR image. For analysis of striatal [$^{123}$I]IBZM binding, three consecutive horizontal slices (total thickness approximately 1.2 mm) with the highest striatal binding were selected. The landmarks for positioning were the intra-orbital glands, striatum, and the borders of the brain. Striatal binding ratios are expressed as specific striatal binding (striatal binding minus cerebellar binding) divided by cerebellar binding.

Ex vivo measurements were performed at the end of experiments 2 and 3. Mice were sacrificed by bleeding via heart puncture under anesthesia. The brain was removed, and striatum and cerebellum were dissected. Radioactivity was measured in a gamma counter, and data were expressed as percent ID per gram tissue.

### Statistics

The Wilcoxon signed rank test was used to analyze the effect of amphetamine administration on [$^{123}$I]IBZM binding, and non-parametric correlation testing was used to compare in vivo with ex vivo data. Comparison of i.p. with i.v. administration was done with a repeated measures general linear model and post hoc Wilcoxon signed rank tests for each time point. Mann–Whitney *U* tests and partial correlation have been used to compare the in vivo and ex vivo data.

## Results

### [$^{123}$I]IBZM dose and pharmacokinetics

Intense, symmetrical [$^{123}$I]IBZM binding was observed in the striatum of control mice (Fig. 1). Around 90 min post-injection peak specific striatal binding ratios were reached (Fig. 2). Highest specific striatal binding was observed with the highest [$^{123}$I]IBZM dose (70 MBq). However, two out of five mice that received this dose died within a few minutes after injection with symptoms of acute alcohol intoxication. After doses of 40 or 20 MBq, no symptoms of acute alcohol intoxication were observed nor did any mouse die. Therefore, in further studies in which the radiotracer was administered intravenously, a dose of 40 MBq was used.

### Amphetamine-induced dopamine release

In this experiment, two mice died within 1 min after the mixture of anesthetics were administered. In one mouse, the radiotracer was accidentally administered paravenously. Therefore, data is presented on a group of six mice.

At baseline, specific striatal [$^{123}$I]IBZM binding ratios were 1.43±0.22 (mean ± standard deviation), and these ratios were significantly reduced (1.03±0.40) after administration of amphetamine (−27.2%; Wilcoxon signed rank test, $n$=6, z=1.992, $p$=0.046; Fig. 3a). In vivo measurements showed good correlation with ex vivo measurements (Spearman's rho=0.943, $n$=6, $p$=0.005, two-tailed; Fig. 3b).

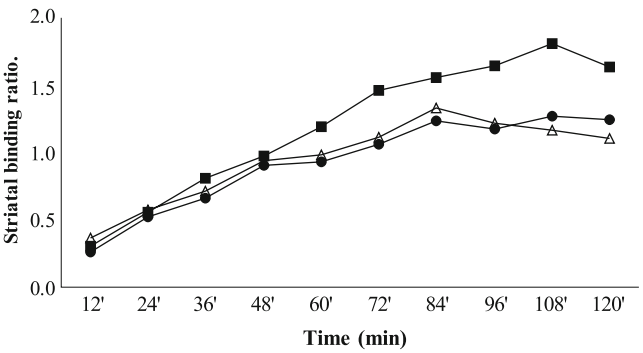


**Fig. 2** Average striatal binding ratio over time of different doses of [$^{123}$I]IBZM administered intravenously in mice. *Solid squares* 70 MBq ($n$=3), *open triangles* 40 MBq ($n$=2), *closed circles* 20 MBq ($n$=2)

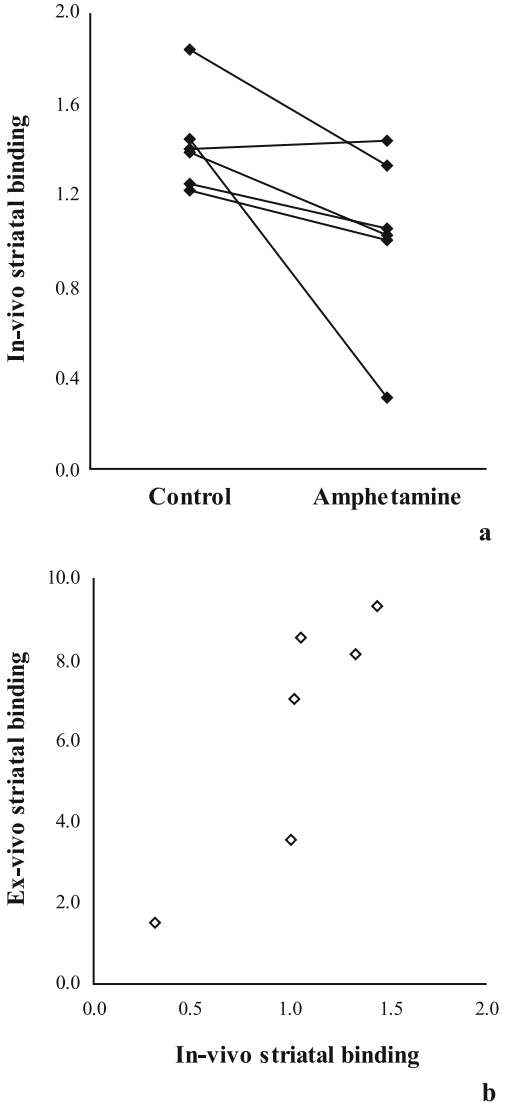


**Fig. 3** **a** In vivo SPECT measurement of striatal binding ratio of [$^{123}$I]IBZM in mice shows a reduction in specific binding after amphetamine administration (Wilcoxon signed rank test $p$=0.046). **b** The in vivo SPECT measurement of specific striatal [$^{123}$I]IBZM binding after amphetamine administration shows good correlation (Spearman's rho=0.943; $p$=0.005) with ex vivo gamma count data

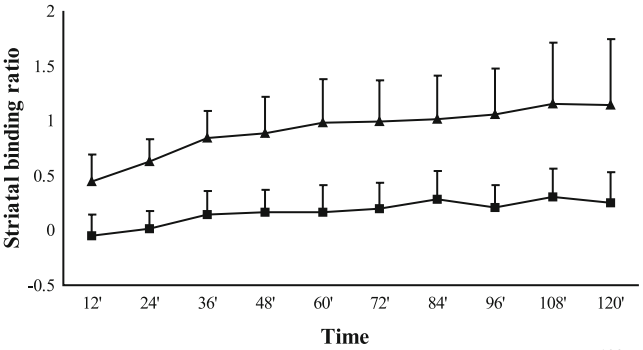


**Fig. 4** Time course of mean specific striatal binding ratios of [$^{123}$I] IBZM (40 MBq) after intravenous (*triangles*) and intraperitoneal (*squares*) administration in nine animals measured in vivo with pinhole SPECT. *Error bars* indicate standard deviation

### Intraperitoneal versus intravenous injection of [$^{123}$I]IBZM

Statistical analysis using a repeated measures general linear model showed that i.v. administration of 40 MBq [$^{123}$I] IBZM led to significantly higher specific striatal binding compared to i.p. administration ($df$=1, $F$=25.62, $p$=0.001, Fig. 4). At each time point, the average striatal binding after i.p. administration was lower than after i.v. administration (paired $t$ tests, $df$=8, $t$≥3.759, $p$≤0.006 at all time points; Wilcoxon signed rank tests, $n$=9, $z$>2.55, two-tailed, $p$≤ 0.011 at all time points). For all mice, both in vivo SPECT data and ex vivo gamma counter data were available. In vivo ROI-based SPECT measurements correlated with ex vivo organ counts corrected for differences in delivered dose (partial correlation=0.784, $df$=10, $p$=0.003, two-tailed). In all animals, ex vivo measurements gave higher specific striatal binding than in vivo measurements (Table 1, Fig. 5). Ex vivo measurements of administration of 40 MBq [$^{123}$I]IBZM i.v. showed higher specific binding than i.p. administration of the same dose (Mann–Whitney $U$ test, $n$=9, $z$=2.449, $p$=0.014). To test whether the lower specific binding measured after i.p. administration could be compensated for by using the high dose, the data for i.p. injection of 70 MBq [$^{123}$I]IBZM were compared with the data for i.v. injection of 40 MBq [$^{123}$I]IBZM. This showed similar specific striatal binding in ex vivo measurements (i.p.= 5.44, i.v.=6.05, Mann–Whitney $U$, $n$=9, $z$=0.735, $p$=0.462), and slightly lower binding after i.p. injection in in vivo measurements (i.p.=0.53, i.v.=1.23, Mann–Whitney $U$ test, $n$=9, $z$=1.960, $p$=0.050).

## Discussion

This paper shows the feasibility of measurements of D2R availability in mice using [$^{123}$I]IBZM single pinhole SPECT imaging. I.v. administration of a dose of 40 MBq [$^{123}$I]IBZM to mice leads to clear visualization of specific binding within the striatum with maximum specific binding ratios reached at 90 min post-injection. We have shown that

**Table 1** Specific striatal binding ratios of [$^{123}$I]IBZM measured in vivo with pinhole SPECT and ex vivo with a gamma counter

| Route of administration | [$^{123}$I]IBZM Dose | $N$ | Mean specific striatal binding ratios (SD) | |
|---|---|---|---|---|
| | | | In vivo | Ex vivo |
| I.v. | 40 MBq (in 0.2 ml) | 5 | 1.23 (0.57) | 6.05 (1.13) |
| I.p. | 40 MBq (in 0.2 ml) | 4 | 0.20 (0.36) | 0.72 (0.68) |
| I.p. | 70 MBq (in 0.35 ml) | 4 | 0.53 (0.16) | 5.44 (1.69) |

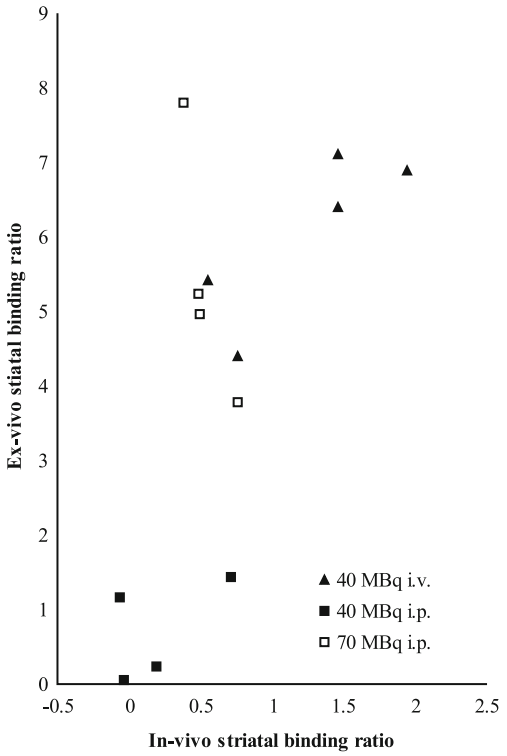


**Fig. 5** Specific striatal binding of different doses of [$^{123}$I]IBZM measured in vivo and ex vivo after intravenous (*i.v.*) or intraperitoneal (*i.p.*) administration is shown for individual mice

[$^{123}$I]IBZM SPECT imaging can be used to measure drug-induced changes in synaptic dopamine in mice in vivo. Interestingly, the observed 27% reduction in [$^{123}$I]IBZM binding after amphetamine-induced release of endogenous dopamine nicely corresponds to the 25% reduction in [$^{11}$C] raclopride binding in rats measured with microPET using the same dose of amphetamine [7]. The 27% reduction in specific binding after administration of a dose of 2.5 mg/kg amphetamine seems rather minor compared to the massive dopamine release after amphetamine administration measured using microdialysis in previous studies [1, 11]. The SPECT measurement is performed 2 h after amphetamine administration at that moment the effect of the amphetamine administration may already be reduced. Competitive inhibition of radioligand binding is the most commonly used postulate to explain reductions in D2R binding after amphetamine administration, but other mechanisms such as dopamine D2R internalization or changes in receptor affinity could attribute as well [12, 13]. To assess the ability to detect amphetamine-induced dopamine release in mice, all mice received amphetamine approximately 1 week after the baseline [$^{123}$I]IBZM SPECT study. In future studies, the design of this sub-study could be improved by alternating the order of [$^{123}$I]IBZM injections alone and the injection of both amphetamine and [$^{123}$I]IBZM.

In the used SPECT system, the animal is placed in a tight-fitting horizontally positioned rotating cylinder. Because of the tight fitting of the animal in the cylinder, in none of our studies, including earlier cardiac studies, have we observed any rotation-induced motion. We have used an MR image of a single mouse for ROI definition and manually registered the ROIs to every SPECT image. Using individual MR images and an automated registration procedure may increase the accuracy of the ROI definition. Currently, the three consecutive slices with highest striatal or cerebellar binding are used for the in vivo calculation of specific binding ratios, whereas the ex vivo measurements are based on whole organ count data. This may explain part of the variation observed in in vivo measurements. The higher ratios found ex vivo than in vivo are mainly caused by the partial volume effect. Furthermore, the used SPECT system has a single pinhole, which limits the amount of radiation that can be detected, resulting in a low sensitivity to small changes in radioligand binding. Future use of a multi-pinhole system such as the U-SPECT [14, 15], which was not available to us at the lab where the studies were conducted, are expected to greatly enhance the detail within the obtained images, as well as increase sensitivity, decrease measurement variation, and decrease the required tracer dose.

An important issue with small animal imaging studies involves the question whether the injected dose corresponds to a pharmacological rather than a tracer dose. For tracer studies, one assumes that occupancy of receptors by the radiotracer should be less than 3% [16]. In the present study, similar to previous dopamine transporter studies [10, 17], we have used doses of which we were confident that they would not violate the pharmacological threshold. Indeed, in a study on D2R imaging in mice with [$^{123}$I]IBF SPECT, Acton and colleagues [18] also argued that due to the high specific activity of SPECT tracers, the occupancy of D2R due to the dose of radiotracer may be minimal. Another issue with the use of [$^{123}$I]IBZM is that ethanol was used as a preparative aid for routine production by the manufacturer, resulting in a final concentration of 8% *v*/*v* ethanol. Even with the very high activity concentration used here, a volume of 0.3 to 0.35 ml is needed to administer a dose of 70 MBq. Administration of 0.3 ml 8% *v*/*v* ethanol (with a specific weight of 0.791 g/ml gives 19 mg ethanol) i.v. to a mouse of 25 g, with a blood volume of approximately 6–8% of its bodyweight, could amount to a peak blood ethanol level of around 19 mg/(25 g×0.08)= 9.5 ‰. This probably explains the high mortality rate immediately after i.v. administration of the 70 MBq dose. I.p. administration may offer a way to circumvent the high peak blood ethanol levels. Given that ethanol rapidly distributes within the body water (taken to be 70% of body weight) injection of 0.3 ml results in a final blood ethanol level of around 19 mg/(25 g×0.7)=1.1‰. Indeed, after administration of 70 MBq of [$^{123}$I]IBZM in 0.35 ml i.p., no signs of acute ethanol intoxication were observed. However, in our experi-

ments, we observed that the specific binding after i.p. administration is much lower than after i.v. administration. An explanation may be that not all injected activity enters the bloodstream after i.p. injection, for example, because part of the administered [$^{123}$I]IBZM dose stays within an area with low blood perfusion or because significant non-specific binding within the abdominal cavity occurs. These issues need to be addressed further before i.p. injection can be adopted as an alternative route of administration. An alternative that may prevent high peak blood alcohol levels when administering high doses of [$^{123}$I]IBZM is the use of a bolus/constant infusion approach [18]. This approach also offers the advantage of performing measurements at true equilibrium.

The in vivo measurement of endogenous dopamine release in mice is of relevance to unravel the high variability in DA release between mice, as well as the causes of disturbances in DA release in addiction. The D2R has been implicated in cocaine addiction, as well as cocaine craving, in humans [19–22]. Therefore, the D2R may provide a target for prevention of relapse after cocaine detoxification, and the study of striatal D2R availability in mouse models of cocaine addiction is important to unravel its role in human cocaine addiction. Repeated measurements within a single mouse enable the differentiation between drug-induced changes [18] and pre-existing differences in D2R availability, as well as offer the possibility to relate these differences to individual variation in drug self-administration. [$^{123}$I]IBZM SPECT imaging will also enable the monitoring of treatment directed at normalizing D2R levels in drug addiction. Furthermore, the ability to measure D2R availability in mice in vivo provides the opportunity to study the involvement of this dopamine receptor in obesity and neuropsychiatric disorders [23, 24]. In this paper, we have demonstrated the feasibility of [$^{123}$I]IBZM pinhole SPECT imaging for repeated in vivo measurements of D2R availability in mice. Improvements in [$^{123}$I]IBZM imaging are expected with improved tracer preparation and with new multi-pinhole SPECT instrumentation that recently entered the market.

**Acknowledgments** We would like to thank Dr. Louk J.M.J. Vanderschuren for his critical reading of the manuscript and his useful comments.

The research was funded by a grant from the University Medical Center Utrecht and the Academic Medical Center.

The experiments comply with the laws of the Netherlands and were approved by the Committee for Animal Care of the Academic Medical Center. The authors have no conflict of interest.

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