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Validity of in vivo [^{123}I]β-CIT SPECT in detecting MDMA-induced neurotoxicity in rats

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Abstract

This study investigated the ability of a high-resolution pinhole single-photon emission computed tomography (SPECT) system, with [^{123}I]β-CIT as a radiotracer, to detect 3,4-methelenedioxymethamphetamine (MDMA, 'Ecstasy')-induced loss of serotonin transporters (SERTs) in the living rat brain. In vivo striatal and thalamic [^{123}I]β-CIT binding ratios, representing specific binding to dopamine and serotonin transporters, respectively, were determined 7 days before as well as 10 days after treatment of rats with neurotoxic doses of MDMA using SPECT. At the end of the experiment, radioactivity ratios were also determined ex vivo, and compared to control data. Both in vivo and ex vivo, thalamic, but not striatal, uptake ratios were statistical significantly reduced after MDMA treatment. These data show that [^{123}I]β-CIT SPECT may be able to detect MDMA-induced loss of SERTs. Therefore, this may be a promising technique to perform serial studies on MDMA-induced serotonergic neurotoxicity in living small animals.
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1. Introduction

3,4-Methelenedioxymethamphetamine (MDMA, 'Ecstasy') is a recreational drug of abuse frequently used among young adults. In line with a human necropsy study (Kish et al., 2000), neurotoxic effects of MDMA on the serotonergic system have been described extensively in MDMA-treated animals, as evidenced by reductions in various markers unique to serotonin (5-HT) axons, including density of 5-HT transporters (SERTs) (Ricaurte et al., 2000). Since the SERT is located on the terminals of presynaptic axons of 5-HT neurons, it is considered to be a reliable marker of 5-HT neurons.

With [^{123}I]β-CIT, a radioligand that binds with high affinity to SERTs and dopamine transporters (DATs), it has become possible to use single-photon emission computed tomography (SPECT) to assess SERT densities in the living brain. The use of [^{123}I]β-CIT in detecting 5-HT lesions has been validated in in vitro and ex vivo studies in rodents (Scheffel et al., 1992; Lew et al., 1996, Reneman et al., 2002). In addition, one SPECT study has been conducted to validate the in vivo use of [^{123}I]β-CIT to detect MDMA-induced loss of SERTs in the SERT-rich midbrain/hypothalamic region in a monkey brain (Reneman et al., 2002). In humans, a [^{123}I]β-CIT SPECT study by Reneman et al. (2001) has shown decreased [^{123}I]β-CIT binding in SERT-rich brain regions such as midbrain and thalamus in females with a history of heavy ecstasy use. In male ecstasy users, however, no alteration of [^{123}I]β-CIT binding in SERT-rich brain regions were found (Semple et al., 1999; Reneman et al., 2001). Reductions of SERT in cortical brain regions, with relatively low concentrations of SERTs, were found in male (Semple et al., 1999) and female (Reneman et al., 2001) ecstasy users.

An animal model of the serotonergic system is of intense interest to study experimentally the influence of different conditions (e.g. temperature and dosing patterns) on neurotoxic effects of MDMA. Moreover, the presumed

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neuroprotective properties of different drugs, such as serotonin transporter reuptake inhibitors, could be tested experimentally. Due to recent developments it is now possible to image rat brains with high-resolution using positron emission tomography (PET) (for review see Myers and Hume, 2002) and SPECT (Acton et al., 2002; Scherfler et al., 2002). One of the most compelling advantages of using in vivo imaging in rats over many ex vivo techniques is the fact that the rat can survive the study and consequently serial studies within the same rat can be performed.

The recent development of a high-resolution single pinhole SPECT camera in our laboratory (Habraken et al., 2001) has made it possible to image monoamine transporters in vivo in small animals. Studies by Booij et al. (2002) have shown that this technique is able to detect reductions in striatal DAT densities in rats.

The objective of the present study was to investigate whether the small animal SPECT scanner is able to detect MDMA-induced loss of SERTs in the living rat brain using [^{123}I]β-CIT as a radiotracer.

2. Experimental procedures

Seven days before treatment with MDMA, a baseline SPECT scan was made. Ten days after final MDMA treatment a post-treatment scan and ex vivo biodistribution studies were performed. In addition, ex vivo biodistribution studies were performed in a control group.

2.1. Animals and drug treatment

Male Wistar rats ($n = 11$, obtained from Harlan, Horst, The Netherlands) weighing 200–250 g were used for this study. The rats were housed in a temperature-controlled environment and were on a 12-h light/12-h dark cycle with free access to food and water. The local Animal Care Committee approved the experiments. MDMA hydrochloride (certified reference compound, purity > 98.9%) was obtained from The Netherlands' Forensic Institute. A frequently used and known neurotoxic dose regimen in Wistar rats is 20 mg/kg s.c. twice a day during 4 days (Ricaurte et al., 2000). However, this schedule was abandoned because two out of six rats died after the first treatment (macroscopic examination showed that one rat died of multiple cerebral haemorrhages, while the cause of death of the other rat could not be detected). The resulting four rats were treated with MDMA 20 mg/kg once a day on the first 2 days, 10 mg once a day on the third day, and 10 mg/kg twice a day on the fourth day.

2.2. In vivo SERT imaging, single-pinhole SPECT camera, MRI

^{123}I-labeling of β-CIT was performed by oxidative radioiododestannylation (Radionuclide Center, Vrije University, Amsterdam, The Netherlands) of the trimethylstannyl precursor (specific activity >185 MBq/nmol; radiochemical purity >97%). Rats were injected with approximately 75 MBq [^{123}I]β-CIT in the tail vein. Scanning was started 2 h p.i., when equilibrium of the SERT binding in rats is

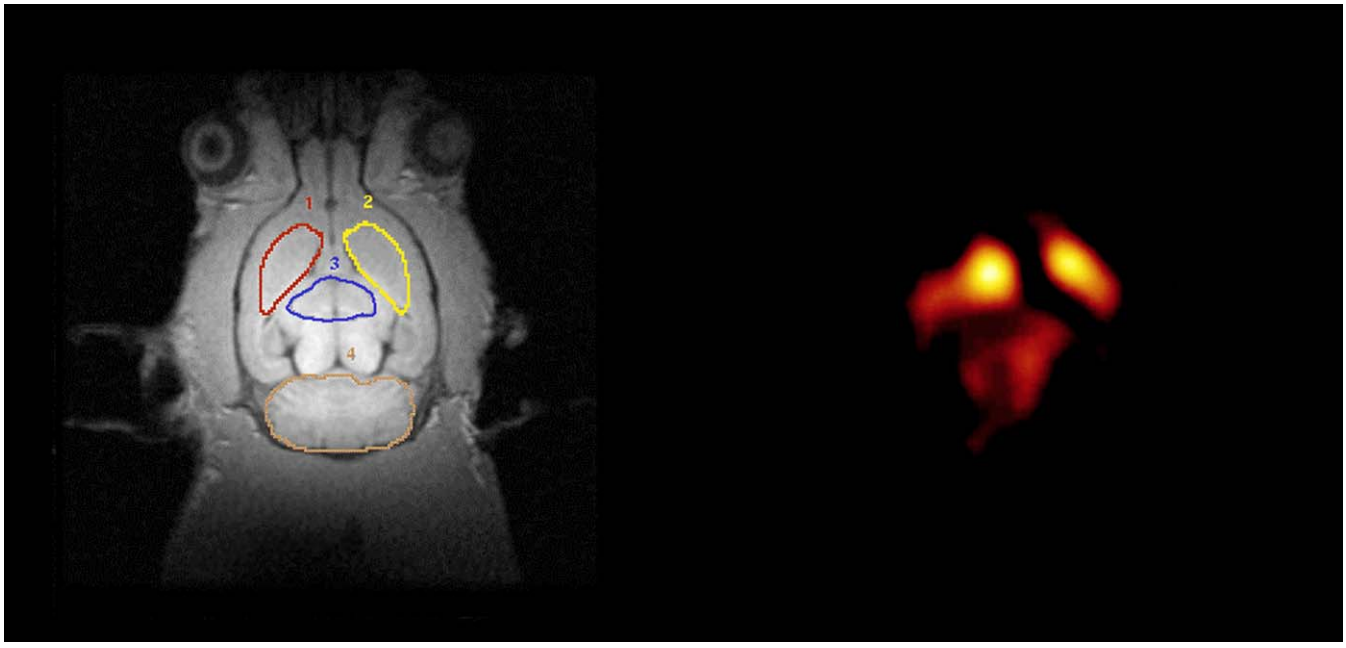

Fig. 1. MR and [^{123}I]β-CIT SPECT image of horizontal slices of rat brain at the level of the striatum with ROI template of right striatum (1), left striatum (2), thalamus (3), and cerebellum (4). The level of radioactivity is colour encoded from low (black) through medium (yellow) to high (white) and scaled to the maximum of the study.

Table 1
Ex vivo and in vivo binding of [^{123}I]β-CIT in striatum, thalamus and cerebellum of the rat brain

	Striatum		Thalamus		Cerebellum	
	Control ($n=5$)	MDMA ($n=4$)	Control	MDMA	Control	MDMA
Ex vivo	74.21	54.73	16.78	10.31	4.56	3.49
(% ID × kg/g	51.79	69.63	17.25	6.73	4.71	3.59
tissue)	88.80	63.89	21.92	6.70	7.24	3.18
	89.67	87.67	19.50	10.19	5.07	4.10
	83.17		20.80		4.74	
Mean	**77.53 ± 15.65**	**68.98 ± 13.89**	**19.25 ± 2.22**	**8.48 ± 2.04**[†]	**5.26 ± 1.12**	**3.59 ± 0.38**[†]
	16.27	15.68	3.68	2.95		
Ex vivo						
Ratios*	11.00	19.40	3.66	1.87		
	12.27	20.09	3.03	2.11		
	17.69	21.38	3.85	2.49		
	17.55		4.39			
Mean	**14.95 ± 3.12**	**19.14 ± 2.45**	**3.72 ± 0.49**	**2.35 ± 0.47**[†]		
	Before MDMA	After MDMA	Before MDMA	After MDMA		
In vivo	2.12	1.78	1.81	1.16		
Ratios*	1.74	1.89	1.45	1.14		
	2.31	2.48	1.71	1.56		
	2.26	1.86	1.59	1.29		
Mean	**2.11 ± 0.26**	**2.00 ± 0.32**	**1.64 ± 0.16**	**1.29 ± 0.19**[‡]		

*Ratios are expressed as uptake in the region of interest divided by cerebellar uptake.
[†]Significant difference from control (Student *t*-test).
[‡]Significant difference from before MDMA treatment (paired Student *t*-test).

approached (Reneman et al., 1999). During scanning, rats were anaesthetised by a mixture of ketamine–HCl and xylazine i.m. The SPECT system has previously been described extensively (Habraken et al., 2001). In the present study, a pinhole with a 2-mm aperture was used, resulting in a spatial resolution of 2.6 mm full-width at half-maximum (FWHM). Data acquisition included 100 projections of 30 s each. All experiments were acquired, in a step-and-shoot fashion, with a 20% energy window around 159 keV in a 128 × 128 matrix, and a radius of rotation of 45 mm. SPECT studies were reconstructed and analysed using HERMES application software (Nuclear Diagnostics, Stockholm, Sweden).

Image analysis was performed using region of interests (ROIs). ROIs for striatum, thalamus and cerebellum were drawn on high-resolution MR images of a rat brain, performed with a 1.5 Tesla scanner (GE Signa-Lx), using a T1 weighted three-dimensional fast-spoiled gradient echo sequence. For this purpose, a special receive-only surface coil was constructed with a diameter of 20 mm, fixed on a Delrin® support (Flick Consulting, The Netherlands). A FOV of 4 × 4 cm and a slice thickness of 0.7 mm in a 256 × 160 × 46 matrix were used. The ROIs were positioned without changing the size and form, on three and two consecutive SPECT slices, visualising most intense striatal and thalamic uptake, respectively, with help of the anatomical information from both MR images as well as a rat brain atlas. MRI anatomical information was used to position ROIs over two consecutive SPECT slices containing cerebellar uptake. [^{123}I]β-CIT binding in the striatum and thalamus was analysed using the ratio of total binding in the ROI divided by non-specific binding (= binding in cerebellum).

2.3. Ex vivo SERT binding studies

Control rats ($n=5$) were injected i.v. with approximately 3.7 MBq [^{123}I]β-CIT. Three hours after injection of [^{123}I]β-CIT in control rats and directly after [^{123}I]β-CIT SPECT scanning (also 3 h after injection) in MDMA-treated rats (10 days after MDMA treatment, $n=4$), animals were sacrificed by bleeding via heart puncture under anaesthesia. The brains were quickly removed and striatum, thalamus and cerebellum were dissected and weighed. Radioactivity in each region was assayed in a gamma counter as described earlier (Rijks et al., 1996) and expressed as a percentage of the injected dose, multiplied by the body weight per gram tissue weight (%ID × kg/g tissue). Additionally, binding ratios in the ROI versus non-specific binding (in cerebellum) were calculated.

2.4. Statistics

Results of the in vivo SPECT study of the remaining four rats were analysed using a Student *t*-test for paired samples. Data from ex vivo SERT biodistribution studies were analysed using a Student *t*-test for two independent samples. Statistical significance was defined as $P<0.05$.

3. Results

MR images showed clear visualisation of striatum, thalamus, cortex and cerebellum of the rat brain (Fig. 1). On the SPECT images, [^{123}I]β-CIT binding was clearly visible in the thalamus, a brain region known to have high concentrations of SERTs (Fig. 1). In addition, high accumulation of [^{123}I]β-CIT was visible in the striatum, predominantly reflecting binding to DATs, whereas cerebellar uptake was very low. Uptake ratios before MDMA treatment were 1.64 and 2.11 in thalamus and striatum, respectively. After MDMA treatment, the thalamic binding ratio of [^{123}I]β-CIT was significantly reduced by 21% ($P=0.044$), whereas the striatal binding ratio did not change significantly (-2%, $P=0.534$) (Table 1).

Ex vivo SERT biodistribution studies in control rats show most intense uptake in the striatum (Table 1). In the thalamic area, the amount of uptake was much lower than in the striatum, whereas the uptake was lowest in the cerebellum. Total [^{123}I]β-CIT uptake was significantly reduced by 56% in the thalamus ($P<0.001$) and by 32% in the cerebellum ($P=0.026$), whereas total striatal uptake did not change significantly (-11%, $P=0.421$). Ratios of [^{123}I]β-CIT uptake in the ROI over uptake in the cerebellum were significantly reduced by 37% in the thalamus ($P=0.004$), but not significantly increased by 28% in the striatum ($P=0.065$).

4. Discussion

Results of both in vivo [^{123}I]β-CIT SPECT studies, as well as the ex vivo biodistribution studies, show that treatment of rats with neurotoxic doses of MDMA lead to significant reductions in the SERT-rich thalamic region. This confirms and extents previous in vitro, ex vivo and in vivo studies in which [^{123}I]β-CIT was found to be able to adequately detect 5-HT lesions (Scheffel et al., 1992; Lew et al., 1996; Reneman et al., 2002). The observed reduction in thalamic [^{123}I]β-CIT SPECT binding ratios, without significant change in striatal binding ratios, likely reflects serotonergic and not dopaminergic neurotoxicity, because it is generally agreed that [^{123}I]β-CIT predominantly labels SERT in the midbrain/thalamus, while DAT in the striatum. Displacement studies in humans and monkeys with [^{123}I]β-CIT (Laruelle et al., 1993; Pirker et al., 1995) and the PET analog [^{11}C]β-CIT (Farde et al., 1994) showed that specific DAT inhibitors displaced β-CIT in the striatum but not in the midbrain, whereas specific SERT inhibitors displaced β-CIT in the midbrain, but not in the striatum. Moreover, other studies have documented reductions in SERT densities, in animals with known MDMA-induced 5-HT injury, while leaving DAT densities unaffected (Battaglia et al., 1987; Ricaurte et al., 2000). In mice, serotonin neurons are spared and dopamine neurons are affected after MDMA administration, possibly caused by species dependent mechanisms (Logan et al., 1988). Only one recent study reported dopaminergic neurotoxicity in primates, probably related to the recreational dose regimen of repeating administration of relatively small doses of MDMA in short time intervals (Ricaurte et al., 2002).

Reneman et al. (2002) have previously shown thalamic [^{123}I]β-CIT binding ratios to be reduced by 59% in ex vivo biodistribution studies in MDMA-treated rats, while in the present study thalamic binding ratios were reduced by 37% in ex vivo, and by 21% in in vivo SPECT studies. This difference in ex vivo binding ratios between the two studies is probably related to the lower doses of MDMA administrated in the present study. Ex vivo binding ratios for thalamus and striatum were much higher than ratios measured in vivo. This is likely to be caused by the partial volume problem induced by measuring radioactivity in the small volume of the thalamus and striatum of rats (Hoffman et al., 1979).

In control rats, the biodistribution study showed most intense uptake of radioactivity in the striatum, with much lower uptake in the thalamus. In the cerebellum, the uptake was lowest, even approximately 5% of striatal uptake. Such a pattern of uptake is in line with previous characterization studies of [^{123}I]β-CIT (Laruelle et al., 1993). Due to the extreme low uptake of β-CIT in the cerebellum, most [^{123}I]β-CIT SPECT studies have used the cerebellum as a region representing non-specific binding. Interestingly, the present biodistribution study shows that, although the total cerebellar [^{123}I]β-CIT binding was low in control rats, it was significantly reduced in MDMA-treated rats. There is evidence that the rat cerebellum is innervated by 5-HT axons and that it therefore contains SERT, although in a low concentration (D'Amato et al., 1987). A recent PET study showed small but significant specific binding of radiotracers that binds to SERTs in monkey cerebellum (Szabo et al., 2002). Since cerebellar [^{123}I]β-CIT uptake in human studies is generally used as a reference for non-specific uptake, and binding ratios are expressed as total binding divided by cerebellar binding, our present finding may indicate, if replicated in human brain, that reductions in binding ratios underestimate reductions in SERT and consequently neurotoxicity. However, since this study is performed in small groups of animals and the cerebellar uptake of [^{123}I]β-CIT is extreme low and therefore prone to low reproducibility, our relevant finding of reduced [^{123}I]β-CIT uptake in the cerebellum needs to be confirmed in larger studies.

The present observation that [^{123}I]β-CIT pinhole SPECT may be useful in studying in vivo MDMA-induced neurotoxic changes is of interest for a number of reasons. It enables to perform serial studies in MDMA-treated small animals in an experimental setting, without the need of sacrificing the animals after each experiment. It may therefore be suitable especially for examining potential confounders that are almost impossible to study experimentally in humans, like effects of temperature and (de)hydration, dosing patterns, age, the effects of combined use of other drugs

of abuse on the neurotoxic action of MDMA and the effects of potential neuroprotective agents like selective serotonin reuptake inhibitors and anti-oxidants. Besides, it may be possible to study long-term effects of MDMA administration on cognitive functioning (Taffe et al., 2002) in older animals in a more accurate way, linking it to temporal changes in SERT and/or DAT densities.

Additionally it may become possible to study in vivo in an experimental setting other diseases with known involvement of the serotonergic system, like depression and anxiety disorders.

Finally, with optimalisation of the co-registration of MR with SPECT images by using external radioactive markers (Scherfler et al., 2002), it will become possible in future studies to examine also brain regions containing low concentrations of SERTs, like the cerebral cortex and hippocampus.

In conclusion, our preliminary ex vivo and in vivo results provide evidence that it is possible to detect MDMA-induced loss of SERTs in the living rat brain by using [^{123}I]β-CIT SPECT. The newly developed high-resolution pinhole SPECT technique may be a promising technique for performing serial studies of MDMA-induced serotonergic neurotoxicity, and other diseases involving the serotonergic system, in living small animals.

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