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BRIEF ARTICLE

Preclinical Safety Assessment of the 5-HT_{2A} Receptor Agonist PET Radioligand [^{11}C]Cimbi-36

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Abstract

Purpose: [^{11}C]Cimbi-36 was recently developed as an agonist radioligand for brain imaging of serotonin 2A receptors (5-HT_{2A}) with positron emission tomography (PET). This may be used to quantify the high-affinity state of 5-HT_{2A} receptors and may have the potential to quantify changes in cerebral 5-HT levels *in vivo*. We here investigated safety aspects related to clinical use of [^{11}C]Cimbi-36, including radiation dosimetry and *in vivo* pharmacology.

Procedures: [^{11}C]Cimbi-36 was injected in rats or pigs, and radiation dosimetry was examined by *ex vivo* dissection or with PET scanning, respectively. Based on animal data, the Organ Level INternal Dose Assessment software was used to estimate extrapolated human dosimetry for [^{11}C]Cimbi-36. The 5-HT_{2A} receptor agonist actions of [^{11}C]Cimbi-36 *in vivo* pharmacological effects in mice elicited by increasing doses of Cimbi-36 were assessed with the head-twitch response (HTR).

Results: The effective dose as extrapolated from both rat and pig data was low, 7.67 and 4.88 μSv/MBq, respectively. In addition, the estimated absorbed radiation dose to human target organs did not exceed safety levels. Administration of 0.5 mg/kg Cimbi-36 leads to significant HTR compared to saline, whereas 0.05 mg/kg Cimbi-36 (doses much larger than those given in conjunction with a PET scan) did not elicit a significant HTR.

Conclusions: Administration of tracer doses of [^{11}C]Cimbi-36 does not seem to be associated with unusual radiation burden or adverse clinical effects.

Key words: PET, Serotonin receptors, Hallucinogenic, Radiation dosimetry, Head-twitch response, Porcine

Introduction

The biogenic amine and neurotransmitter serotonin (5-HT) is extensively involved in behavioural processing, and dysfunction in the serotonergic neurotransmitter system is relevant in pathophysiology of human diseases including, but not confined to, depression and schizophrenia. The serotonin 2A (5-HT_{2A}) receptor is the most abundant excitatory 5-HT receptor in the human brain, and 5-HT_{2A} receptor stimulation exerts the hallucinogenic effects of drugs such as lysergic acid diethylamide whilst the therapeutic effects of atypical antipsychotics are at least partly

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attributed to the antagonistic effects on these receptors [1]. Where 5-HT_{2A} receptor antagonists bind the total pool of receptors, 5-HT_{2A} receptor agonists bind the high-affinity and G-protein-coupled sub-population of receptors [2]. Thus, compared to the available antagonist radioligands, the binding of a 5-HT_{2A} receptor agonist is hypothesised to yield a more functionally relevant image of the state of the receptors [3]. Currently, it remains to be demonstrated that the 5-HT_{2A} receptor agonist binds selectively to the high-affinity state of 5-HT_{2A} receptors in the living brain. However, some evidence has suggested that receptor agonist *in vivo* binding is functionally more relevant when compared to antagonist binding. For example, positron emission tomography (PET) studies of dopamine 2 receptors have shown that agonist PET tracers are more displaceable by elevated levels of endogenous dopamine as compared to antagonist tracers [4, 5].

PET imaging allows for quantification of neuroreceptors, and with the appropriate PET radioligand, neurotransmitter release can be detected as receptor binding will be inversely correlated to extracellular levels of neurotransmitters such as has been shown for the dopamine system [6]. Thus, PET imaging has the potential to measure serotonin levels in a non-invasive way in the human brain. However, this requires a PET radioligand which is sensitive to changes in serotonin levels, and despite recent progress within imaging of other 5-HT receptors [7–9], a PET radioligand sensitive to fluctuations in endogenous 5-HT levels has yet fully to be evaluated for use in humans [3]. While dysfunction of the serotonergic neurotransmitter system remains highly disease relevant, this is difficult to demonstrate in patients at least partly since no clinically applicable method exists for quantifying 5-HT levels *in vivo*. The disease relevance of the serotonin system infers that measuring endogenous 5-HT release with PET would have great implications for research in human disease, in particular within affective disorders. Since no PET radioligand yet has made such measurements possible, the development of a 5-HT_{2A} receptor agonist PET tracer for clinical studies would be of great importance.

We have recently validated a series of *N*-benzylphenethylamines as agonist PET radioligands for selective mapping and quantification of 5-HT_{2A} receptors *in vivo* [10, 11]. Out of a total of ten radiolabelled compounds tested *in vivo* with PET scanning in the pig brain, [^{11}C]Cimbi-36 was found to possess the best PET tracer properties [11]. Preliminary studies in non-human primates support the notion that [^{11}C]Cimbi-36 binding is reduced by fenfluramine-induced increases in 5-HT levels [12]. In order to allow for [^{11}C]Cimbi-36 to be taken into humans, some safety issues in terms of dosimetry and pharmacological effects need to be addressed. Particularly since most 5-HT_{2A} receptor agonists have potent hallucinogenic effects in humans, the possibility of adverse effect from Cimbi-36 administration needs to be evaluated prior to clinical use of [^{11}C]Cimbi-36.

Here we assess safety issues for the clinical use of [^{11}C]Cimbi-36, including dosimetry and *in vivo* pharmacology in rodents. The head-twitch response (HTR) in rodents is a well-validated behavioural proxy of the hallucinogenic effect of 5-HT_{2A} receptor activation in humans and can be used as a behavioural parameter to distinguish hallucinogenic from non-hallucinogenic 5-HT_{2A} receptor agonists [1]. As a proxy for hallucinogenic effects, we use the HTR assay in mice to estimate effective doses of Cimbi-36-induced receptor activation. Furthermore, we estimate the radiation dosimetry related to clinical [^{11}C]Cimbi-36 use based on radioligand uptake measurements using an *ex vivo* dissection method in rats and *in vivo* PET/CT scanning in pigs.

Materials and Methods

Synthesis of Cimbi-36 and [^{11}C]Cimbi-36

Non-radioactively labelled Cimbi-36 for use in the pharmacological experiments and as a reference compound for the radiolabelling was synthesised as follows: triethylamine (1.0 mmol) was added to a suspension of 2-(4-bromo-2,5-dimethoxyphenyl)ethanamine hydrochloride (1.0 mmol) and 2-methoxybenzaldehyde (1.1 mmol) in ethanol (10 ml), and the reaction was stirred until formation of the imine was complete according to thin-layer chromatography. Sodium borohydride (2.0 mmol) was added and the reaction was stirred for another 30 min. The reaction mixture was concentrated under reduced pressure and partitioned between dichloromethane and water (30 ml, 1:1). The organic layer was isolated and the aqueous layer was extracted with dichloromethane (2×15 ml). The combined organic extracts were dried with sodium sulphate, filtered and evaporated under reduced pressure. The residue was purified by flash chromatography (dichloromethane/methanol/ammonia 98:2:0.04). The purified free base was dissolved in ethanol (2 ml), ethanolic hydrogen chloride (1 M, 2 ml) was added and the solution was diluted with diethyl ether until crystals formed. The crystals were collected by filtration and dried under reduced pressure to give Cimbi-36 in 85 % yield as a colourless solid. Structural identity was confirmed by nuclear magnetic resonance spectroscopy.

[^{11}C]Cimbi-36 (chemical structure in Fig. 1) was produced by methylation of its *N*-Boc-protected precursor using ^{11}C-methyl triflate as previously described [11].

Ex Vivo Distribution in Rats

Whole body [^{11}C]Cimbi-36 biodistribution was examined in 16 adult male Sprague Dawley rats (mean weight, 287±11 g). The animals were injected with 21.6±8.3 MBq [^{11}C]Cimbi-36 intravenously (i.v.) in the tail vein and decapitated after 5, 15, 30 and 60 min. After decapitation, 14 distinct tissues, including liver, stomach wall, spleen, kidney, adrenal glands, lung, heart wall, bone, adipose tissue, testis, muscle, blood, frontal cortex and cerebellum were taken

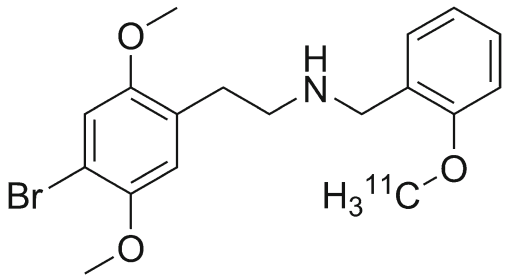

Fig. 1. Molecular structure of [^{11}C]Cimbi-36. The compound has high affinity (K_i=1.01 nM) and is a highly selective 5-HT$_{2A}$ receptor agonist PET tracer [11].

out and weighed. All rodent studies and procedures were approved by the Danish Council for Animal Ethics (journal no. 2007/561-1320). Tissue radioactivity concentration was measured in a gamma counter (in kBq/g) (Cobra 5003, Packard Instruments), divided by the injected dose (ID) to yield percent ID per gram and further multiplied by animal weight (in gram), thus yielding unitless values corresponding to standardized uptake values (SUV) in quantity.

Distribution in Pigs Measured by PET/CT

A total of four female Danish Landrace pigs (mean weight, 20.3±1.5 kg) were used in this study. After arrival, animals were housed under standard conditions and were allowed to acclimatize for 1 week before scanning. On the scanning day, pigs were tranquilized by intramuscular (i.m.) injection of 0.5 mg/kg midazolam. Anaesthesia was induced by i.m. injection of a Zoletil veterinary mixture (1.25 mg/kg tiletamin, 1.25 mg/kg zolazepam and 0.5 mg/kg midazolam; Virbac Animal Health). Following induction, anaesthesia was maintained by i.v. infusion of 15 mg/kg/h propofol (B. Braun Melsugen AG). During anaesthesia, animals were endotracheally intubated and ventilated (volume, 250 ml; frequency, 15/min). Venous access was granted through two Venflons (Becton Dickinson) in the peripheral milk veins, and an arterial line for blood sampling was inserted in the femoral artery after a minor incision. [^{11}C]Cimbi-36 was given as an i.v. bolus injection (ID, 434±105 MBq; injected mass, 4.0±2.7 μg), and the pigs were subsequently scanned for 120 min with a GE Discovery LS PET/CT scanner (GE Healthcare, Milwaukee, WI) in 2D mode. Scanning was started at the time of injection. In all pigs, arterial whole blood samples were manually drawn at 2.5, 5, 10, 20, 30, 40, 50, 70, 90 and 120 min, and radioactivity in whole blood and plasma was measured using a well counter (Cobra 5003, Packard Instruments) that was cross-calibrated to the PET scanner. Immediately after scanning, animals were sacrificed by i.v. injection of pentobarbital/lidocain. The pig studies and procedures were approved by the Danish Council for Animal Ethics (journal no. 2007/561-1320).

The PET acquisition covered six bed positions of 15 cm, repeated 14 times with increasing duration, (2×30, 5×60 and 7×120 s per bed position). Images were reconstructed using a filtered back-projection algorithm (Hann 6-mm filter) including attenuation and scatter correction. Regions of interest (ROI), including brain, lungs, heart, muscle (backside), liver, spleen, ventricle, intestines, kidneys, bladder and bone (hind leg), were drawn directly on the CT image using the in-house custom-made software EditRoi (implemented in Matlab v. 7.12, Mathworks Inc., Natick, MA, USA), thereby overlaying them to the PET image. Activity in all ROIs was extracted as the average of radioactive concentration (in kilobecquerel per cubic centimetre). Radioactive concentration in ROI (in in kilobecquerel per cubic centimetre) was normalized by the ID divided by animal weight, in kilobecquerel per gram, thus yielding SUV in the unit of gram per cubic centimetre. Mean time for each time frame was used as a representation in the time–activity curves.

Human Dosimetry Estimation

The human absorbed doses for [^{11}C]Cimbi-36 were extrapolated from both rat and pig data using the Organ Level INternal Dose Assessment (OLINDA) software [13]. Residence times (in hour) for [^{11}C]Cimbi-36 in each pig and rat tissue were calculated from the area under curve (AUC) of the non-decay-corrected time-activity curves. The tissue activity in the first time point was assumed to constitute the activity from t=0 to this point. From the radioactive concentration in the last time point ($A_{120\ \mathrm{min}}$ for pigs, $A_{60\ \mathrm{min}}$ for rats), extrapolation by physical decay was done. Thus, $A_{120\ \mathrm{min}}/k$ (where k equals the decay constant for C-11) was added to the AUC to extrapolate the integral radioactivity to infinity. The AUC of the tissue radioactivity concentrations from rats and pigs was scaled to human values by multiplication with the fractional organ weights of the standard human phantom as previously described [14]. Extrapolated human residence times were used as input for the OLINDA calculations. For the rat data, where no radioactivity in urine or bile was measured, assumptions regarding hepatobiliary and renal excretion were applied similarly to what was done in previous studies [15]. As a result, 21 % of the total radioactivity was transferred to the gastrointestinal tract model, and 22 % cleared to the bladder with a $t½$ of 17 min. For the pig data, measured radioactivity after [^{11}C]Cimbi-36 injection in the pig bladder and gall bladder was used as the contents of these organs.

HTR Analysis in Mice

To assess the pharmacological effects of 5-HT$_{2A}$ receptor stimulation, the HTR was assessed in mice by giving various doses of Cimbi-36. Forty NMRI mice (standard outbred strain from Taconic, Ejby, Denmark; mean weight, 39±3 g) were injected intraperitoneally (i.p.) with saline, 2,5-dimethoxy-4-iodoamphetamine (DOI) dissolved, or increasing doses of Cimbi-36 dissolved in saline. The animals were

video filmed for 25 min after injection, and HTR (distinctive shaking movement of the head, visible as rapid movement of the ears) was counted by a blinded observer for 20 min starting 5 min after injection.

Results

Whole Body Distribution of [^{11}C]Cimbi-36

The whole body *ex vivo* biodistribution of [^{11}C]Cimbi-36 in rats revealed that the lungs had the highest uptake of the tissues examined (SUV ~30); this peaked at the first time point (5 min) and declined hereafter (Fig. 2b). In the PET/CT scan of the pig, high activity was also found in the lungs, where it also displayed a fast washout (Fig. 2a). In pigs, however, the highest [^{11}C]Cimbi-36 uptake was found in excretory organs (bladder, gall bladder and kidneys) and the decay-corrected uptake in these organs was highest in the later time frames indicating that [^{11}C]Cimbi-36 excretion occurs through both the hepatobiliary and renal–urinary pathways (Fig. 3). For all non-excretory tissues examined in both rats and pigs, the uptake peaked and declined within the time frame of the experiments indicative of reversible uptake in these tissues. A peak total brain uptake of [^{11}C]Cimbi-36 was found at ~1.5 SUV in both rats and pigs.

Human Dosimetry Extrapolated from Rat and Pig Data

The human target organ with the highest absorbed dose extrapolated from both rat and pig data was the urinary bladder wall (Table 1). The effective human doses as extrapolated from animal data from both species were low (4.88 μSv/MBq when extrapolated from pig data, 7.67 μSv/MBq when extrapolated from rat data). Thus, human subjects undergoing [^{11}C]Cimbi-36 PET scans with typical amounts of injected activity would receive around 2–4 mSv. In conjunction to PET brain studies, [^{11}C]Cimbi-36 has been given i.v. without observation of any general effects in the anaesthetized animals. In the pigs, vital signs were monitored during the PET scans, and no adverse effects on blood pressure, pulse, saturation or electrocardiogram were observed.

In Vivo Pharmacological Effects of Cimbi-36

After i.p. administration of 0.5 mg/kg Cimbi-36 and 2.5 mg/kg DOI, the mice displayed comparable and significant HTR relative to saline (Fig. 4). A significant HTR was not elicited by 0.05 mg/kg Cimbi-36 relative to saline, while Cimbi-36 doses at and above 2.5 mg/kg had prominent sedative effects. Thus, significant pharmacological effects were not observed at dosages much greater than those given in conjunction with a PET scan, i.e. 50 μg/kg did not produce significant HTR in mice.

Discussion

Our previous studies have demonstrated that [^{11}C]Cimbi-36 is a promising 5-HT$_{2A}$ receptor agonist PET radioligand in pigs and in an affinity screening against multiple neuroreceptors revealed that Cimbi-36 is highly selective for 5-HT$_2$ receptors [11]; subsequent studies have found that the radioligand possesses even better signal-to-noise ratios in monkeys [12]. Therefore, brain imaging studies in humans with [^{11}C]Cimbi-36 are warranted, and the present studies address safety aspects related to the clinical use of this radioligand.

In both rats and pigs, [^{11}C]Cimbi-36 uptake in the lungs was high, and in both animal species, lung kinetics were similar, with an initial peak uptake and a rapid washout from tissue. The brain uptake in pigs of [^{11}C]Cimbi-36 was found to be in accordance with previous studies (peak SUV ~1.5) [11], and similar brain uptake was found in rats, while the [^{11}C]Cimbi-36 brain uptake in non-human primates is slightly higher [12]. In the later time frames, [^{11}C]Cimbi-36 accumulated in the excretory tissues (gall bladder, kidney and urinary bladder) of the pig indicating that the PET radioligand is excreted through both the hepatobiliary and renal–urinary pathways. This indicates validity of the excretory assumptions made for the rat data where radioactivity is transferred to both pathways.

The values of effective dose (4.9 μSv/MBq extrapolated from pig data and 7.7 μSv/MBq from rat data) are only slightly higher than the value of 4.5 μSv/MBq reported by ICRP for a generic C-11 receptor ligand model [16], the tissue showing major increases as compared to the model being lung, liver and kidney. However, the extrapolated values for [^{11}C]Cimbi-36 effective doses are well in line with an average value of 5.9±2.0 μSv/MBq found in a meta-analysis of radiation dosimetry studies of 37 carbon-11-labelled small molecules [17]. Thus, in terms of radiation doses received in conjunction with PET scanning of humans with [^{11}C]Cimbi-36, use of this tracer is associated with levels of absorbed doses in the same range as other clinically applied ^{11}C-radioligands, such as [^{11}C]Raclopride or [^{11}C]DASB [17]. With these radioligands, the study participant is normally informed that PET scanning with one radioligand injection would be associated with an effective dose approximately corresponding to 1 year's background radiation.

Furthermore, the effective doses extrapolated from animal data are expected to be fairly predictive of human values: from an average of multiple C-11-labelled PET radioligands where radiation dosimetry studies have been conducted in both animals and humans, no systematic deviation in the effective doses was found [17]. However, discrepancies between human dosimetry extrapolated from animal data and dosimetry data from clinical studies have previously been reported for certain PET radioligands such as the α_7 nicotinic receptor ligand [^{11}C]CHIBA-1001 and the 5-HT$_{1A}$ receptor ligand [^{11}C]WAY100635. But these differences

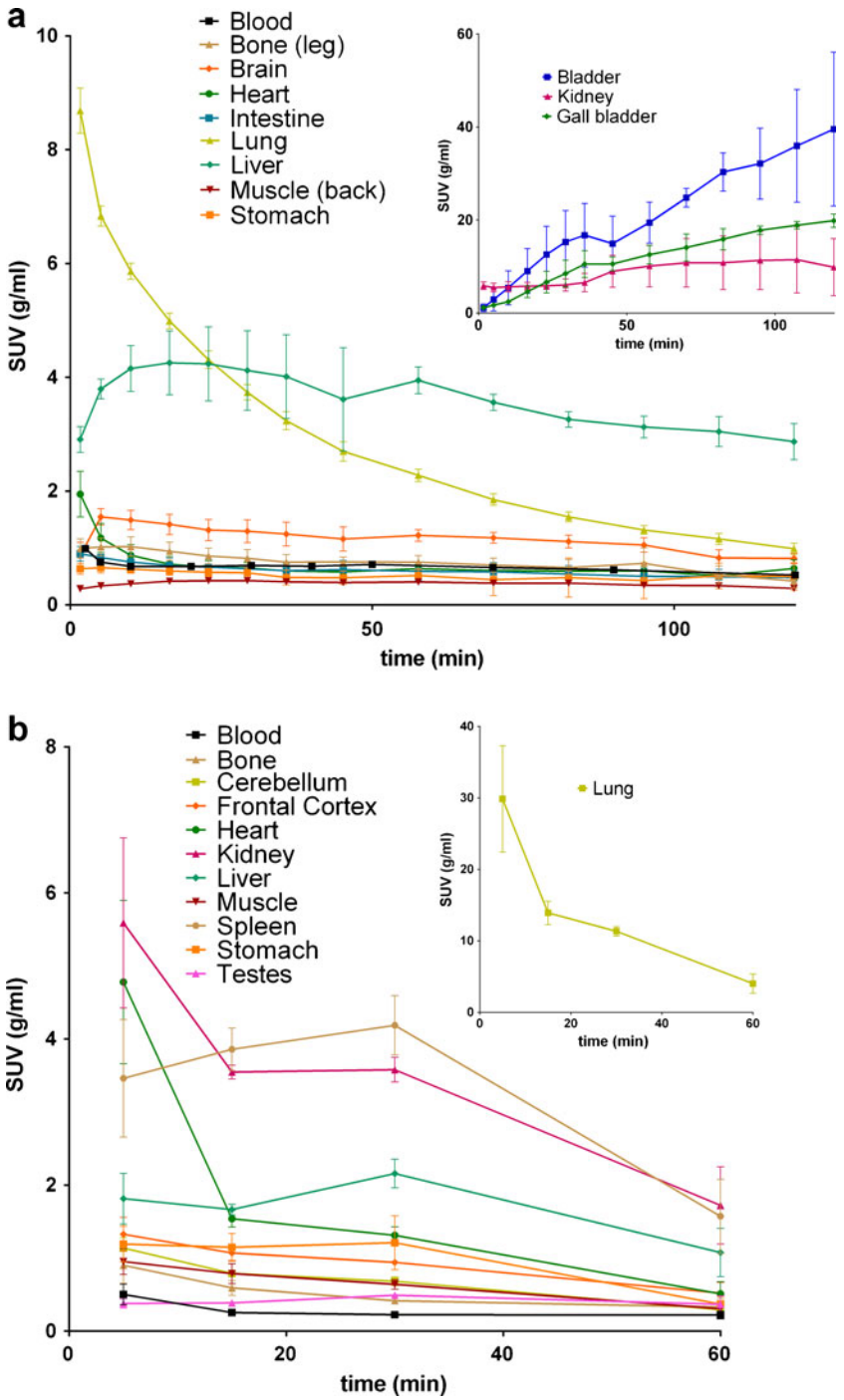

Fig. 2. Whole body tissue distribution of [^{11}C]Cimbi-36 in pigs (**a**) and rats (**b**). The decay-corrected tissue radioactivity is shown as SUVs. **a***In vivo* distribution of radioactivity following [^{11}C]Cimbi-36 injection in four Danish Landrace pigs scanned in a PET/CT scanner. The *insert* shows the tissue involved in radioligand excretion: kidney, bladder and gall bladder. **b** Average *ex vivo* rat tissue radioactivity from four rats for each time point (5, 15, 30 and 60 min). The *insert* shows the radioactive concentration of [^{11}C]Cimbi-36 in rat lungs. Mean ± SEM are shown for each time point.

were not substantial enough to alter the conclusions regarding the safety of application of the PET radioligands in humans. The estimates of effective doses are important for PET centres in the EU since this value determines the maximal allowable injectable activity per study [17].

Despite large differences in methodology between the two dosimetry studies, the estimated human radiation doses calculated from the two studies were in good accordance. Different animal species were used, rats and pigs; different detection methods were applied, PET scanning and ex vivo dissection; different time courses of examined radioactivity,

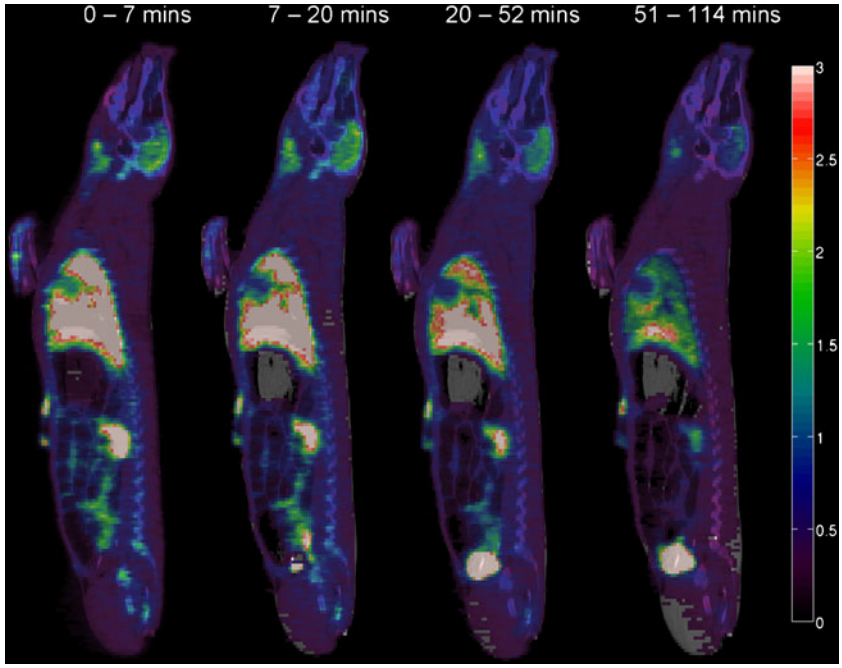

Fig. 3. Representative image of [^{11}C]Cimbi-36 in whole body pig scans. Sagittal whole body PET images of [^{11}C]Cimbi-36 distribution in a pig. Images are averaged over the indicated time interval and overlaid the corresponding section in the CT image. Images are scaled to SUVs as given by the *colour bar*. PET images are threshold so that voxels with SUV values lower than 0.2 % of the maximal voxel value are cut off.

60 and 120 min; the pigs were anaesthetized using propofol while an *ex vivo* dissection study was performed in awake rats and assumptions regarding radioligand excretion were applied since radioactivity in the rat urine was not quantified. However, although both animal studies yielded fairly coherent estimates of human dosimetry, [^{11}C]Cimbi-36 dosimetry studies in humans are still needed before routine clinical use of this radioligand to firmly address radiation safety.

Table 1. Estimated human radiation doses extrapolated from rat and pig data

Target organ	Absorbed dose (mGy/MBq)	
	Extrapolated from pig data	Extrapolated from rat data
Adrenals	2.94E−03	7.72E−03
Brain	3.11E−03	2.37E−03
Breasts	1.87E−03	1.24E−03
Gall bladder wall	4.29E−03	2.79E−03
LLI wall	2.76E−03	3.42E−03
Small intestine	4.03E−03	2.86E−02
Stomach wall	2.48E−03	1.90E−03
ULI wall	2.72E−03	1.05E−02
Heart wall	3.22E−03	5.76E−03
Kidneys	1.29E−02	8.28E−03
Liver	9.08E−03	5.08E−03
Lungs	9.44E−03	2.76E−02
Muscle	1.87E−03	2.44E−03
Ovaries	2.82E−03	3.93E−03
Pancreas	2.94E−03	2.14E−03
Red marrow	2.10E−03	1.71E−03
Osteogenic cells	2.89E−03	1.39E−03
Skin	1.60E−03	8.25E−04
Spleen	6.06E−03	7.62E−03
Testes	2.15E−03	1.28E−03
Thymus	2.12E−03	1.63E−03
Thyroid	1.95E−03	1.00E−03
Urinary bladder wall	2.80E−02	3.93E−02
Uterus	3.49E−03	4.52E−03
Effective dose[a]	*4.88E−03*	*7.67E−03*

[a]The unit of effective dose is mSv/MBq

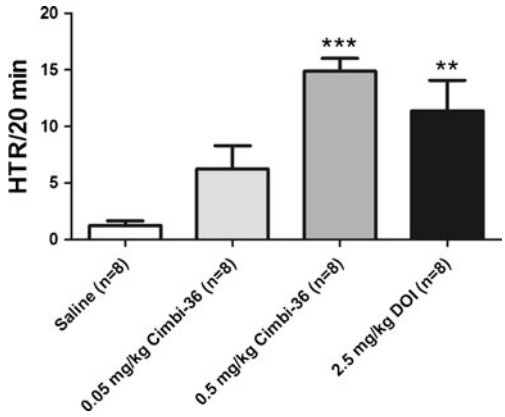

Fig. 4. Cimbi-36 induces HTRs in a dose-dependent manner in mice. NMRI mice were injected i.p. with 0.9 % saline, 2.5 mg/kg DOI or Cimbi-36 in various concentrations. $^{**}p<0.01$, $^{***}p<0.001$ vs. saline in a one-way ANOVA with Tukey's post-test for multiple comparisons.

Since most 5-HT$_{2A}$ receptor agonists have potent hallucinogenic effects in humans, the possibility of adverse effect from Cimbi-36 administration needs to be evaluated. Furthermore, the HTR in mice is a well-validated surrogate marker of the hallucinogenic effect of 5-HT$_{2A}$ receptor activation in humans and can be used as a behavioural parameter to distinguish hallucinogenic from non-hallucinogenic 5-HT$_{2A}$ receptor agonists [1]. Therefore, we assessed the *in vivo* pharmacological effect of Cimbi-36 administration in mice. We show that Cimbi-36 elicits a prominent HTR in a high dose of 0.5 mg/kg. This demonstrates that Cimbi-36 has similar properties *in vivo* as the reference 5-HT$_{2A}$ receptor agonist DOI. Thus, the agonist properties of Cimbi-36 which previously were demonstrated in activation studies *in vitro* [11] are confirmed *in vivo* after i.p. injections in mice. To our knowledge, the *in vivo* efficacy of *N*-benzyl substituted phenethylamines has not previously been demonstrated, although many compounds in this class have been shown to be highly potent 5-HT$_{2A}$ receptor agonists *in vitro* [11, 18]. Since the HTR in rodents is tightly linked to the hallucinogenic effect in humans, it is highly likely that Cimbi-36 in sufficient doses will result in hallucinations in humans. However, in the current experiment in mice, 0.05 mg/kg Cimbi-36 i.p. did not elicit a significant HTR, indicating that this dose in mice was not sufficient to yield *in vivo* effects. Despite this, DOI is reported to be an active hallucinogen in man at oral doses of 1.5–3.0 mg [19], and the present results (that 0.5 mg/kg Cimbi-36 and 2.5 mg/kg DOI caused similar HTR) suggest that Cimbi-36 is more potent than DOI. So extrapolated crudely to human doses, this suggests that human oral doses of 300–600 μg Cimbi-36 should yield significant hallucinations. Even though such a direct extrapolation to a human dose rarely is accurate, the mass doses given in conjunction to a PET scanning are usually in the low microgram range. Injected cold mass of 1 μg in a 70-kg human subject corresponds to 14 ng/kg or approximately 3,500-fold lower than the dose presently found to cause only a non-significant increase in HTR in rodents and approximately 300-fold lower than the dose expected to cause hallucinations in humans. So even though such extrapolations of *in vivo* efficacy between species should be made with caution, these data still suggest that subjects will not experience hallucinations following administration of Cimbi-36 in the tracer amounts received during a PET scan.

Conclusions

The extrapolated effective dose of [^{11}C]Cimbi-36 was 5–8 μSv/MBq which is similar to that of most other C-11-labelled neuroreceptor PET radioligands, and PET studies are thus not associated with prohibitively high levels of radiation dosimetry. Furthermore, the cold mass of Cimbi-36 received in tracer dose administration is much lower than those doses associated with pharmacological effects in rodents, and [^{11}C]Cimbi-36 can therefore be administered safely in relation to PET scanning.

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Conflict of Interest. The authors declare that they have no conflict of interest.

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