BRIEF ARTICLE

First Evaluation of [11C]R116301 as an *In Vivo* Tracer of NK1 Receptors in Man

Saskia P. A. Wolfensberger,[1,2] Bart N. M. van Berckel,[1] Anu J. Airaksinen,[1,4] Kaoru Maruyama,[1,5] Mark Lubberink,[1] Ronald Boellaard,[1] William D. H. Carey,[3] Wieb Reddingius,[3] Dick J. Veltman,[1,2] Albert D. Windhorst,[1] Josée E. Leysen,[1,3] Adriaan A. Lammertsma[1]

[1]Department of Nuclear Medicine & PET Research, VU University Medical Centre, P.O. BOX 7057, 1007 MB, Amsterdam, The Netherlands
[2]Department of Psychiatry, VU University Medical Centre, Amsterdam, The Netherlands
[3]Johnson & Johnson Pharmaceutical Research & Development, Beerse, Belgium
[4]Present address: Laboratory of radiochemistry, University of Helsinki, Helsinki, Finland
[5]Present address: Department of Nuclear Medicine and Tracer Kinetics, Osaka University Graduate School of Medicine, Osaka, Japan

Abstract

Purpose: NK1 receptors have been implicated in various neuropsychiatric and other disorders. R116301 is a selective NK1 receptor antagonist. In this pilot study, [11C]R116301 was evaluated as a potential positron emission tomography (PET) ligand for the NK1 receptor.

Procedures: Two dynamic PET studies were performed in three normal volunteers before and after a blocking dose of aprepitant. Data were analyzed using striatum to cerebellum standardized uptake value (SUV) ratios.

Results: Baseline SUV ratios at 60–90 min after injection ranged from 1.22 to 1.70. Following aprepitant administration, this specific signal was completely blocked. Aprepitant administration did not significantly affect uptake in cerebellum, confirming the absence of NK1 receptors in cerebellum.

Conclusion: These preliminary results indicate that [11C]R116301 has potential as a radioligand for *in vivo* assessment of NK1 receptors in the human brain.

Key words: NK1 receptor, [11C]R116301, PET, SUV

Introduction

Tachykinins are a class of neuropeptides that are involved in a variety of biological functions in the central and peripheral nervous systems [1–3]. Tachykinin receptors have been divided into three subtypes according to their preferred ligands: neurokinin 1 (NK1), NK2, and NK3. NK1 receptors, for which substance P has the highest affinity, have been of particular interest because of their potential implication in various neuro-psychiatric and other disorders. Autoradiography studies of the brain of various species have demonstrated the presence of NK1 receptors in several cerebral structures with the highest density in striatum [4] and negligible density in cerebellum [5]. NK1 antagonists

could potentially be used for treating a variety of disorders [6–8]. Originally, selective nonpeptide antagonists of the NK1 receptor were studied as potential analgesic compounds [9]. Several studies have provided evidence that NK1 receptor antagonists might be effective in the treatment of anxiety disorders and depression [10–13], although a recent clinical study in depression could not confirm these findings [14]. The highly selective NK1 antagonist aprepitant [14], 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorphenyl)-4-morpholinyl]methyl]-1,2-dihydro-3H-1,2,4-triazol-3-one, however, is effective in the treatment of nausea and emesis after chemotherapy and is already in routine clinical use as an anti-emetic agent [15, 16]. To assess novel drugs targeting the NK1 receptor, development of a positron emission tomography (PET) tracer for this target is warranted, as this would provide a unique *in vivo* means of measuring receptor occupancy. In addition, *in vivo*

Correspondence to: Adriaan A. Lammertsma; *e-mail:* aa.lammertsma@vumc.nl

imaging studies might provide new possibilities for studying the role of the NK1 receptor in neuro-psychiatric disorders.

Although several NK1 agonists and antagonists have been labeled successfully for *in vitro* use, to date, most attempts to develop tracers for *in vivo* imaging studies have not been successful [17–19]. For example, although the radioiodinated selective NK1 antagonist L-703606 was useful for labeling NK1 receptors *in vitro* [20], it failed to provide a specific signal *in vivo* in rat and monkey [21]. For the high affinity antagonist [^{11}C]GR205171, promising results were obtained in monkeys [22], providing images that reflected specific binding to NK1 receptors. Its use was limited, however, by the fact that it did not reach equilibrium within 90 min, which is close to the maximum scanning time possible with a carbon-11 labeled ligand. Recently, [2-[^{18}F] fluoromethoxy-5-(5-trifluoromethyltetrazol-1-yl)benzyl]-([2S,3S]-2-phenylpiperidin-3-yl)-amine ([^{18}F]SPARQ) was developed as a fluorine-18 labeled alternative. SPARQ is structurally related to GR205171 and is a selective high-affinity antagonist of the NK1 receptor [4, 21, 23]. Unfortunately, in areas with high receptor densities, [^{18}F] SPARQ only reached equilibrium after 6 h, limiting its use for clinical or intervention studies [5]. In addition, plasma kinetics of [^{18}F]SPARQ were fast, and 90 min after injection, the amount of parent compound in blood was too low to be measured reliably [5]. As such, at present there is no "ideal" tracer for human NK1 receptors and, therefore, alternative compounds need to be investigated.

N1-(2,6-Dimethylphenyl)-2-(4-{(2R,4S)-2-benzyl-1-[3,5-i(trifluoromethyl) benzoyl]hexahydro-4-pyridinyl}pipera-zino)acetamide (R116301) is an orally active, potent, and selective nonpeptide NK1 receptor antagonist with a K_i of 0.45 nM against human NK1 receptors [24]. The affinity for human NK2 and NK3 receptors is 1,600- and 230-fold lower, respectively. At high concentrations, R116301 interacts with rat Na$^+$ and Ca^{2+} ion channel binding sites ($K_i >$ 2 μM), but it does not interact with other receptors, ion channels, or transporter sites at a concentration of 10 μM. R116301 suppresses various aspects of substance P induced behavior *in vivo* and behaves as a full antagonist *in vitro* [25]. Recently, R116301 was labeled with carbon-11 [24]. The present study is the first application of [^{11}C]R116301 in humans. The aim of the study was to evaluate presence of selective [^{11}C]R116301 binding to the NK1 receptor *in vivo*.

Materials and Methods

Subjects

Three healthy subjects, two men aged 46 and 42 and one woman aged 25, were included. Subjects were studied within 21 days after eligibility screening, which consisted of medical history including Structured Clinical Interview for DSM-IV Axis I disorders [26], history of alcohol and drug abuse, physical examination, vital signs and electrocardiogram, laboratory (blood and urine) assessments, and extensive drugs (of abuse) screening. The female subject was practicing an effective method of birth control, and

pregnancy tests were performed at screening and on the day of the study. Volunteers were medication-free for at least 14 days prior to PET scanning. In addition, subjects underwent a structural magnetic resonance imaging (MRI) scan within 14 days prior to the actual PET study to exclude any clinically significant abnormalities and for coregistration with the PET images. The study was approved by the Medical Ethics Committee of the VU University Medical Centre. Subjects gave written informed consent prior to entering the study.
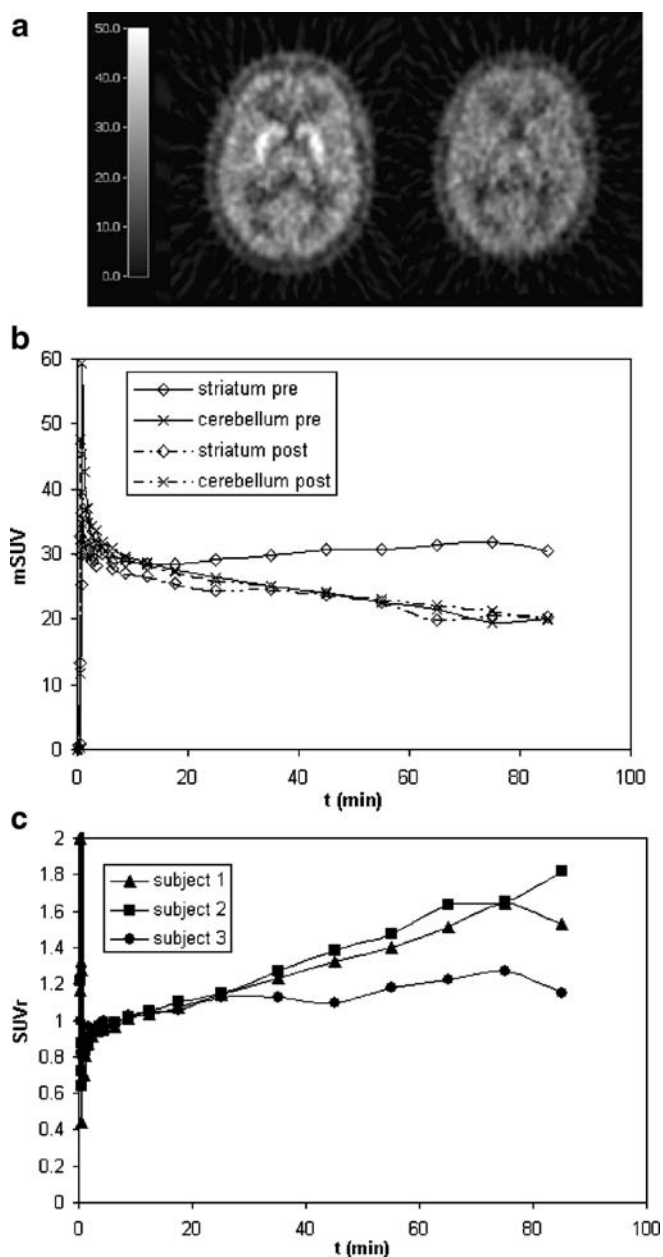
Fig. 1. **a** [^{11}C]R116301 SUV images (60–90 min post injection) for subject number 1, before (*left*) and 3.5 h after (*right*) oral administration of 125 mg aprepitant. **b** Pre- and post-aprepitant SUV curves for striatum and cerebellum of subject 1. **c** Pre-aprepitant striatum to cerebellum SUVr. Note that SUV is normalized to body surface area and that results are expressed as milliSUV (mSUV).

Scanning Protocol

Each PET session consisted of two [11C]R116301 scans on the same day, separated by 5 h. [11C]R116301 was synthesized as described previously [24]. The first scan was under baseline conditions, while the second was performed 3.5 h after a single oral dose of 125 mg of the NK1 antagonist aprepitant (EMEND®). Pretreatment with 125 mg aprepitant is expected to nearly block specific uptake of [11C]R116301, as it has been reported that this dose leads to an occupancy of NK1 receptors of more than 90% [4].

PET scans were acquired using an ECAT EXACT HR+ PET scanner (Siemens/CTI, Knoxville, TN, USA) [27]. All subjects received an indwelling radial artery cannula for arterial sampling. After a 10 min 2D transmission scan, used to correct the subsequent emission scan for tissue attenuation, a 3D dynamic [11C]R116301 scan was performed. This scan consisted of 23 frames with progressive increase in frame duration (1× 15, 3×5, 3×10, 2×30, 3×60, 2×150, 2×300, and 7×600 s), resulting in a total scan duration of 90 min. The mean (±SD) [11C]R116301 tracer dose, administered using an injector (Multilevel CT Injector; Medrad, Pittsburgh, PA, USA), was 427±44 MBq, with a specific activity of 31 ± 7 GBq/µmol.

During the [11C]R116301 scan, arterial blood was monitored continuously using an on-line detection system (Veenstra Insruments, Joure, Netherlands) [28]. In addition, at set times manual blood samples were collected for measurement of metabolite fractions.

Magnetic resonance imaging was performed using a 1.5-T Sonata system (Siemens, Erlangen, Germany) with a standard receiver head coil. For each subject, a coronal 3D gradient-echo T1-weighted sequence (matrix 256×160; inversion time, 300 ms; TR=15 ms; TE=7 ms; flip angle=80; voxel size $1 \times 1 \times 1.5$ mm; 160 sections) was acquired.

Image Analysis

[11C]R116301 scans were reconstructed using a FORE + 2D filtered back projection algorithm [29] and a Hanning filter with a cut-off at 0.5 times the Nyquist frequency, including usual corrections for decay, dead time, attenuation, scatter, and randoms. A zoom factor of 2 and an image matrix size of 256×256 were used, resulting in a final image resolution of ~7 mm full width at half maximum and a voxel size of $1.2 \times 1.2 \times 2.4$ mm^3.

Baseline and post-aprepitant dynamic PET scans were coregistered to each other and subsequently to individual MRI scans using the software package MIRIT [30, 31]. Using anatomical criteria and the three-dimensional software program DISPLAY (http://www.bic.mni.mcgill.ca/software/Display), regions of interest (ROIs) were defined manually on the individual MRI scan for the following structures: caudate, putamen, medial temporal lobe (MTL), thalamus, cingulate, frontal cortex, parietal cortex, insular cortex, occipital cortex, and cerebellum. MRI scans were segmented into grey and white matter and, except for cerebellum, only grey matter voxels within a ROI were used for further analysis [32]. As segmentation in the cerebellum is less accurate, all voxels within the cerebellum ROI were used. Finally, tissue time–activity curves were generated by projecting these ROIs onto all dynamic frames.

Assessment of Specific Signal

During the study, significant sticking of [11C]R116301 to the wall of the polytetrafluoroethylene tubing was suspected, as flushing the line did not result in a reduction of detector counts. This was confirmed in a retrospective experiment, where significant residual activity was measured after rinsing a tube that had been filled with [11C]R116301 containing blood. Due to this sticking, arterial input curves were unreliable, making compartmental analysis impossible. Therefore, for this first analysis, standardized uptake values (SUV) were used. SUV represents the mean (over a time interval) tissue concentration, normalized for injected dose and either subject weight, lean body mass, or body surface area [33]. SUV were obtained for all ROIs of both baseline and post-aprepitant [11C]R116301 scans. As it is known that the level of NK1 receptors is negligible in cerebellum [5], the target to cerebellum SUV ratio (SUVr) was used for estimating the size of the specific signal, and this ratio was also used as outcome parameter for assessing the effects of aprepitant. Emphasis was on striatum, as this structure has the greatest density of NK1 receptors.

Results

Plasma clearance of [11C]R116301 was rapid with no differences between pre- and post-aprepitant scans (data not shown). Due to this rapid plasma clearance, metabolites could not be measured after 60 min. Metabolite fractions (determined using the manual samples) at 40 min post injection ranged from 20% to 45% (average 35%).

As expected, highest uptake was observed in striatum, with intermediate uptake in cortical areas, and lowest uptake in white matter and cerebellum. In Fig. 1a, pre- and post-aprepitant SUV images (60–90 min post injection) are shown for one of the subjects (subject 1), illustrating substantial reduction of [11C]R116301 uptake after aprepitant administration. In contrast to striatum, aprepitant administration did not significantly affect [11C]R116301 SUV in cerebellum, confirming absence of NK1 receptors in cerebellum (Fig. 1b).

Striatum to cerebellum SUVr steadily increased over time but tended to level off after about 60 min post injection (Fig. 1c). Therefore, for assessment of the size of the specific signal, the interval 60–90 min post injection was used.

Baseline striatum to cerebellum SUVr were 1.56, 1.70, and 1.22 and reduced to 0.97, 0.96, and 1.01 post-aprepitant,

Table 1. Pre- and post-aprepitant SUVr (60–90 min post injection), together with their ratio

	Subject 1			Subject 2			Subject 3		
	Pre	Post	Pre/post	Pre	Post	Pre/post	Pre	Post	Pre/post
Striatum	1.56	0.97	1.61	1.70	0.96	1.77	1.22	1.01	1.21
Caudate	1.33	0.85	1.57	1.55	0.86	1.80	1.04	0.92	1.13
Putamen	1.95	1.19	1.64	1.95	1.16	1.69	1.61	1.19	1.35
Thalamus	1.14	0.98	1.16	1.30	1.12	1.16	0.83	1.02	0.81
Frontal Ctx	1.22	1.00	1.22	1.24	1.02	1.22	0.97	0.97	1.00
Cingulate	1.27	1.07	1.19	1.22	1.02	1.20	1.12	1.11	1.00
MTL	1.02	0.91	1.12	1.16	0.97	1.20	1.08	1.02	1.06
Insula	1.25	1.07	1.17	1.18	1.05	1.13	1.11	1.07	1.04
Parietal Ctx	1.24	1.00	1.24	1.24	0.99	1.24	0.93	0.99	0.95
Occipital Ctx	1.29	1.06	1.22	1.29	1.01	1.27	1.14	1.08	1.05

Ctx cortex, *MTL* medial temporal lobe

respectively. Pre- and post-aprepitant SUVr for all ROIs are shown in Table 1, together with their ratio. Note that, in subject number 3, the latter ratio is smaller than 1 for parietal cortex and thalamus, which is probably within measurement error, at least for parietal cortex, although a small movement artifact for thalamus cannot be excluded. More importantly, pre- to post-aprepitant ratios of SUVr ranged from 1.21 to 1.77 for striatum (Table 1).

Discussion

This is the first study using the highly selective novel PET ligand [^{11}C]R116301 in human subjects. The distribution of this tracer corresponds to the known distribution of NK1 receptors, with high retention in striatum (caudate and putamen) and much lower retention in cortical areas [5]. Blocking studies with the NK1 antagonist aprepitant caused a substantial reduction of the specific signal of [^{11}C] R116301 to background levels, confirming selectivity of binding to the NK1 receptor. On the other hand, the rather low target to cerebellum SUVr suggests a relatively high degree of nonspecific binding in humans.

The signal in the cerebellum could not be blocked by aprepitant, confirming that the density of NK1 receptors in human cerebellum is negligible [5]. Consequently, cerebellum can be used as reference region, i.e., as an estimate of free and nonspecific binding. Therefore, for the blocking studies, the ratio of target to cerebellum SUVr relative to baseline was used as outcome measure. The size of the specific signal was assessed at the interval 60–90 min post injection, as SUVr seemed to become fairly constant within this time span.

It should be noted that striatum to cerebellum SUVr for the baseline scan of subject 3 was lower than that of the other two subjects, indicating lower specific binding (Fig. 1c). Subject 3 was, however, screened in the same manner as the other two subjects, and all parameters were within normal range. Although a moderate age effect (7% decrease per decade, significant in other regions than striatum) on NK1 receptor density has been reported [34], both age and gender could not explain this lower binding, as subject 3 was a man of 42 years. With the present sample size, it is not possible to assess whether the observed intersubject variability was due to biology (e.g., polymorphism with modulating effects on affinity of the receptor) or methodology (i.e., effect of using a simple SUVr for quantification). Further studies are needed to address these issues, in particular assessing the validity of using SUVr as outcome measure. In addition, a tracer kinetic model for more quantitative analyses of [^{11}C]R116301 data needs to be developed.

At present, [^{18}F]SPARQ is a PET tracer that provides a much higher specific signal than [^{11}C]R116301. Therefore, at least in theory, it should provide a more accurate assessment of NK1 receptor status or occupancy. Nevertheless, for clinical applications, [^{18}F]SPARQ is far from ideal because of its slow kinetics, requiring very long study durations, thereby increasing the risk of movement artifacts. At the cost of a reduced signal, [^{11}C]R116301 has the advantage that studies can be performed within a reasonable time (90 min).

When ranking the affinity of various NK1 ligands based on pK_i values versus [^{3}H]SP (substance P), the following order (from high to low) is obtained: GR205171 > aprepitant > R116301 > substance P [35]. It is likely that the affinity of SPARQ [5] is higher or equal than that of GR205171. It is clear that the affinity of R116301 is lower than that of SPARQ, which is in agreement with the higher specific signal observed with [^{18}F]SPARQ. On the other hand, the lower affinity of R116301 implies that [^{11}C]R116301 could be more sensitive to differences in endogenous substance P concentrations. This would be very interesting in intervention studies, where release of the endogenous ligand could be manipulated by a pharmacological challenge or, for example, a fear stimulus. Clearly, further studies are needed to establish whether this is feasible.

The NK1 receptor has shown to be an enigmatic target for neuroscience drug discovery and development. To date, antagonists for the NK1 receptor have shown efficacy in the prevention of chemotherapy-induced nausea and vomiting. Although both NK1 receptors and substance P are widely distributed in the brain and may be involved in many neuropsychiatric disorders, many clinical trials on anxiety and depression have found no therapeutic effects of antagonist drugs. Nevertheless, Casopitant® (GlaxoSmith Kline), an NK1 antagonist, is still under clinical investigation for a variety of disorders, including phase II studies in anxiety and depression. Availability of a PET tracer could facilitate further clinical exploration of NK1 receptor involvement in a variety of neuropsychiatric disorders and serve as a tool for the development of drugs that target the NK1 receptor. The present study demonstrates that [^{11}C]R116301 could be a potential candidate tracer for those investigations.

References

1. Otsuka M, Yoshioka K (1993) Neurotransmitter functions of mammalian tachykinins. Physiol Rev 73:229–308
2. Quartara L, Maggi CA (1997) The tachykinin NK1 receptor. Part I: ligands and mechanisms of cellular activation. Neuropeptides 31:537–563
3. Quartara L, Maggi CA (1998) The tachykinin NK1 receptor. Part II: distribution and pathophysiological. Neuropeptides 32:1–49
4. Hargreaves R (2002) Imaging substance P receptors (NK1) in the living human brain using positron emission tomography. J Clin Psychiatry 63 (Suppl 11):18–24
5. Hietala J, Nyman MJ, Eskola I et al (2005) Visualization and quantification of neurokinin-1 (NK1) receptors in the human brain. Mol Imag Biol 7:262–272
6. Farthing MJG (2004) Novel agents for the control of secretory diarrhoea. Expert Opin Investig Drugs Expert 13:777–785

7. Hosoki R, Yanagisawa M, Onishi Y, Yoshioka K, Otsuka M (1998) Pharmacological profiles of new orally active nonpeptide tachykinin NK1 receptor antagonists. Eur J Pharmacol 341:235–241

8. Walpole CSJ, Brown MCS, James IF et al (1998) Comparative, general pharmacology of SDZ NKT 343, a novel, selective NK1 receptor antagonist. Br J Pharmacol 124:83–92

9. De Felipe C, Herrero JF, O'Brien JA et al (1998) Altered nociception, analgesia and aggression in mice lacking the receptor for substance P. Nature 392:394–397

10. Kent JM, Mathew SJ, Gorman JM (2002) Molecular targets in the treatment of anxiety. Biol Psychiatry 52:1008–1030

11. Kramer MS, Cutler N, Feighner J et al (1998) Distinct mechanism for antidepressant activity by blockade of central substance P receptors. Science 281:1640–1645

12. Krishnan KRR (2002) Clinical experience with substance P receptor (NK1) antagonists in depression. J Clin Psychiatry 63:25–29

13. Rupniak NM (2002) Elucidating the antidepressant actions of substance P (NK1 receptor) antagonists. Curr Opin Investig Drugs 3:257–261

14. Keller M, Montgomery S, Ball W et al (2006) Lack of efficacy of the substance P (neurokinin(1) receptor) antagonist aprepitant in the treatment of major depressive disorder. Biol Psychiatry 59:216–223

15. Dando TM, Perry CM (2004) Aprepitant-A review of its use in the prevention of chemotherapy-induced nausea and vomiting. Drugs 64:777–794

16. Hesketh PJ, Grunberg SM, Gralla RJ et al (2003) The oral neurokinin-1 antagonist aprepitant for the prevention of chemotherapy-induced nausea and vomiting: a multinational, randomized, double-blind, placebo-controlled trial in patients receiving high-dose cisplatin-The Aprepitant Protocol 052 Study Group. J Clin Oncol 21:4112–4119

17. Breeman WAP, VanHagen MP, VisserWisselaar HA et al (1996) In vitro and in vivo studies of substance P receptor expression in rats with the new analog [indium-111-DTPA-Arg(1)]substance P. J Nucl Med 37:108–117

18. Delrosario RB, Mangner TJ, Gildersleeve DL et al (1993) Synthesis of a nonpeptide C-11 labeled substance-P antagonist for PET studies. Nucl Med Biol 20:545–547

19. Livni E, Babich JW, Desai MC et al (1995) Synthesis of a C-11 labeled Nk1 receptor-ligand for PET studies. Nucl Med Biol 22:31–36

20. Francis BE, Swain C, Sabin V, Burns HD (1994) Radioiodinated L-703,606—a potent, selective antagonist to the human NK(1) receptor. Appl Radiat Isotopes 45:97–103

21. Solin O, Eskola O, Hamill TG et al (2004) Synthesis and characterization of a potent, selective, radiolabeled substance-P antagonist for NK1 receptor quantitation: ([F-18]SPA-RQ). Mol Imag Biol 6:373–384

22. Bergstrom M, Fasth KJ, Kilpatrick G et al (2000) Brain uptake and receptor binding of two [C-11]labelled selective high affinity NK1-antagonists, GR203040 and GR205171—PET studies in rhesus monkey. Neuropharmacology 39:664–670

23. Bergstrom M, Hargreaves RJ, Burns HD et al (2004) Human positron emission tomography studies of brain neurokinin 1 receptor occupancy by aprepitant. Biol Psychiatry 55:1007–1012

24. Van der Mey M, Janssen CGM, Janssens FE et al (2005) Synthesis and biodistribution of [C-11]R116301, a promising PET ligand for central NK1 receptors. Bioorg Med Chem 13:1579–1586

25. Megens AA, Ashton D, Vermeire JC et al (2002) Pharmacological profile of (2R-trans)-4-[1-[3,5-bis(trifluoromethyl)benzoyl]-2-(phenylmethyl)-4-piper idinyl]-N-(2,6-dimethylphenyl)-1-acetamide (S)-hydroxybutanedioate (R116301), an orally and centrally active neurokinin-1 receptor antagonist. J Pharmacol Exp Ther 302:696–709

26. First MB, Spitzer RL, Gibbon M, Williams JBW (1996) Structured clinical interview for DSM-IV clinical version (SCID-I/CV). American Psychiatric Press, Washington, DC

27. Brix G, Zaers J, Adam LE et al (1997) Performance evaluation of a whole-body PET scanner using the NEMA protocol. J Nucl Med 38:1614–1623

28. Boellaard R, van Lingen A, van Balen SCM, Hoving BG, Lammertsma AA (2001) Characteristics of a new fully programmable blood sampling device for monitoring blood radioactivity during PET. Eur J Nucl Med 28:81–89

29. Defrise M, Kinahan PE, Townsend DW, Michel C, Sibomana M, Newport DF (1997) Exact and approximate rebinning algorithms for 3-D PET data. IEEE Trans Med Imag 16:145–158

30. Maes F, Collignon A, Vandermeulen D, Marchal G, Suetens P (1997) Multimodality image registration by maximization of mutual information. IEEE Trans Med Imag 16:187–198

31. West J, Fitzpatrick JM, Wang MY et al (1997) Comparison and evaluation of retrospective intermodality brain image registration techniques. J Comput Assist Tomogr 21:554–566

32. Zhang YY, Brady M, Smith S (2001) Segmentation of brain MR images through a hidden Markov random field model and the expectation-maximization algorithm. IEEE Trans Med Imag 20:45–57

33. Hoekstra CJ, Paglianiti I, Hoekstra OS et al (2000) Monitoring response to therapy in cancer using [F-18]-2-fluouo-2-deoxy-D-glucose and positron emission tomography: an overview of different analytical methods. Eur J Nucl Med 27:731–743

34. Nyman MJ, Eskola O, Kajander J et al (2007) Gender and age affect NK1 receptors in the human brain-a positron emission tomography study with [F-18]SPA-RQ. J Comput Assist Tomogr 10:219–229

35. Griffante C, Carletti R, Andreetta F, Corsi M (2006) [3H]GR205171 displays similar NK1 receptor binding profile in gerbil and human brain. Br J Pharmacol 148:39–45