

Imaging Substance P Receptors (NK₁) in the Living Human Brain Using Positron Emission Tomography

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Substance P (SP)–neurokinin-1 (NK₁) receptor pathways have been implicated in the pathophysiology of emesis and depression. Autoradiographic studies in monkey and human brains have shown a high expression of NK₁ receptors in regions important for the regulation of affective behaviors and the neurochemical response to stress. Furthermore, clinical studies demonstrated that treatment with the SP (NK₁ receptor) antagonist (SPA) aprepitant (also known as MK-0869) significantly improves depression symptoms and reduces the incidence of chemotherapy-induced nausea and vomiting. An important objective of all neuroscience drug discovery and development programs is to establish the correlation between dose, receptor occupancy, and the observed clinical effect (the dose-response relationship). These goals can be achieved using radioactive receptor-specific tracers and dynamic noninvasive brain imaging modalities, such as positron emission tomography (PET). In the SPA program, a tracer [¹⁸F]SPA-RQ was chosen for PET studies on the basis of several criteria, including high affinity for the NK₁ receptor, low nonspecific binding, and good blood-brain barrier penetration. PET imaging studies in rhesus monkeys and humans confirmed these tracer features and established the usefulness of this probe for in vivo NK₁ receptor occupancy studies. Subsequent PET occupancy studies in humans predicted that very high levels of central NK₁ receptor occupancy (> 90%) were associated with therapeutically significant antidepressant and antiemetic effects. Future PET imaging studies will focus on quantification of NK₁ receptor expression in depressed patients, both before and after successful treatment with antidepressants. (*J Clin Psychiatry* 2002;63[suppl 11]:18–24)

Substance P (SP) is an 11-amino-acid residue molecule that belongs to the group of peptides known as neurokinins (NKs). SP exerts its biological effects by binding to and activating the NK₁ receptor. The SP-NK₁ receptor pathway is the most abundant and the most extensively studied NK pathway in both the central nervous system (CNS) and the peripheral nervous system (PNS),¹ where it plays an important role in the regulation of response to a broad range of inflammatory, noxious, and stressful stimuli. In the spinal cord, SP is thought to be involved in nociception and sensitization “wind-up” phenomena, but clinical studies of SP (NK₁ receptor) antagonists (SPAs) in somatic pain have to date been negative.² High concentrations of SP are also present in the brain stem nuclei, nucleus tractus solitarius, and area postrema, regions that have been implicated in the control of the vomiting reflex.³ A role for SP in the regulation of emesis is further supported by observations that local application

of SP to the area postrema causes retching in ferrets and that the chemotherapeutic agent cisplatin increases plasma levels of SP in cancer patients.⁴ Most importantly, SPAs were recently shown to block emesis in animal models and to prevent acute and delayed chemotherapy-induced nausea and vomiting (CINV) in the clinic.^{5,6}

Receptor mapping studies have shown that the SP-NK₁ receptor system is also expressed in brain regions involved in the regulation of affective behaviors and the neurochemical response to stress.^{7–9} Despite some interspecies differences in the expression of NK receptors,¹⁰ NK₁ receptors predominate in the brain of gyrencephalic species. Specific autoradiographic [¹²⁵I]SP binding studies in human and monkey brains demonstrate the greatest abundance of NK₁ receptors in the amygdala, nucleus accumbens, septum, caudate, and putamen, with moderately high levels in the hippocampus, hypothalamus, locus ceruleus, substantia nigra, and the frontal and olfactory cortices. This observation, together with the significant neuroanatomical spatial overlap of the SP-NK₁ receptor system with that of monoamine neurotransmitter pathways (serotonin [5-hydroxytryptamine {5-HT}] and norepinephrine), suggested that the SP-NK₁ receptor pathway may be involved in the modulation of affective behaviors.

Collective evidence from preclinical and clinical studies with highly selective nonpeptide SPAs further supported this idea. In gerbils, the anxiety-like stress behavior of foot tapping could be induced by central infusion of the NK₁ receptor agonist GR73632 and strongly inhibited by

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several SPAs (aprepitant [also known as MK-0869], its analog L-760735, and a structurally different agent, L-733060).¹¹ Additional studies in guinea pigs further demonstrated that SPAs, such as aprepitant, L-733060, and L-760735, substantially attenuated vocalizations induced by either intracerebroventricular administration of an NK₁ receptor agonist or transient maternal separation, similar to the effects seen with established anxiolytics and antidepressants.¹¹ A phase 2 clinical trial with the orally active SPA aprepitant showed improvements in depression and anxiety symptoms that were quantitatively comparable to those seen with the selective serotonin reuptake inhibitor (SSRI) paroxetine and significantly greater than those seen with placebo.¹¹ These findings provided a proof of concept that SPAs may be a novel class of clinically useful antidepressants.¹¹ Lack of significant antidepressant efficacy with aprepitant versus placebo in a subsequent dose-finding study was uninformative, because the active control (fluoxetine, 20 mg/day) also did not differentiate from placebo.⁴ It should be noted that this absence of significant effect versus placebo has been reported in approximately 50% of trials with various antidepressants.⁴ The validity of the SPA antidepressant concept is supported by 2 independent studies with 3 structurally distinct SPAs (see review by Krishnan in this supplement¹² and Chappell¹³) that have replicated the initial findings with aprepitant.

An important objective in the clinical development of any novel CNS therapy, such as the SPAs, is to establish a clear correlation between the dose or plasma level of the drug and the receptor occupancy achieved. This methodology can be used to guide dosing in efficacy studies, as the achievement of adequate receptor occupancy in proof-of-concept studies is a prerequisite for adequate assessment of efficacy hypotheses. Positron emission tomography (PET) imaging data, together with plasma drug levels in patients, can also be used to examine the dose-receptor occupancy relationship achieved in successful clinical studies and thus to choose dosing regimens for subsequent trials. The recent development of [¹⁸F]SPA-RQ, a radioactive, brain-penetrant, nonpeptide tracer that binds to the NK₁ receptor with high affinity and selectivity, may be particularly useful in this respect, because it permits real-time imaging of receptor occupancy in living human subjects via PET imaging. The tracer permits quantification of NK₁ receptor occupancy with various doses of SPAs and thereby helps to define the degree and duration of receptor occupancy required to achieve consistent antidepressant/antiemetic effects, in turn allowing dose optimization. Furthermore, this tracer may also be useful for monitoring NK₁ receptor density in patients with affective disorders, for investigating the involvement of the SP-NK₁ receptor pathway in the response to currently available therapeutic agents, and for examination of the activity of the SP-NK₁ receptor pathway during remission from depression. The goals of this review are to describe the localization of the

SP-NK₁ receptor system in animals and humans, as determined by autoradiography and PET studies, and to discuss the experience with [¹⁸F]SPA-RQ as a tool to facilitate dose optimization of SPAs for treatment of depression and CINV.

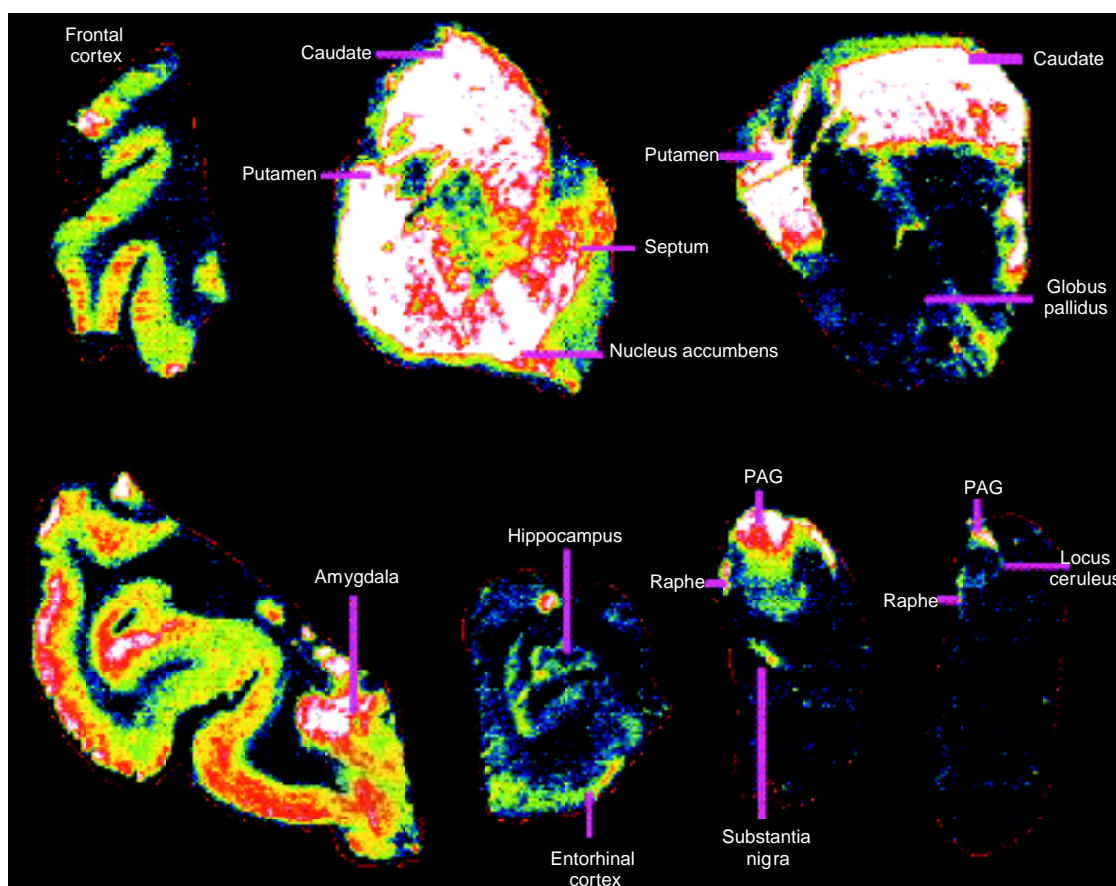
AUTORADIOGRAPHIC STUDIES

Autoradiographic (ARG) studies using [¹²⁵I]SP as an NK₁ receptor probe and [¹²⁵I]leleodoisin as an NK₃ receptor probe in various species (e.g., rat, gerbil, guinea pig, cat, monkey, and human) indicated that the expression of the NK₁ receptor in the CNS is far greater than that of the NK₃ receptor across all species. Moreover, in the monkey and human CNS, the NK₃ receptor is expressed at very low levels, with very limited distribution.^{14,15} It is noteworthy that the NK₂ receptor was not found to be expressed in the brain of gyrencephalic species and that it appeared only transiently during development in rat pups. In the monkey and human brain, [¹²⁵I]SP had the greatest binding in the amygdala, nucleus accumbens, septum, caudate, putamen, hippocampus, hypothalamus, locus ceruleus, substantia nigra, and the frontal, entorhinal, and olfactory cortices. Binding was also observed in the periaqueductal gray (PAG) and the primary monoaminergic nuclei (locus ceruleus: norepinephrine; raphe nucleus: serotonin) (Figure 1). Complete blockade of [¹²⁵I]SP binding in these areas was achieved with an excess of unlabeled SP, confirming the selectivity of the [¹²⁵I]SP for the NK₁ receptors. Additionally, pretreatment with unlabeled SPA specific for the human NK₁ receptor effectively prevented the binding of [¹²⁵I]SP to brain sections from guinea pigs, gerbils, monkeys, and humans, but was much less (more than 30-fold) active in rats. This observation is consistent with the lower affinity of SPAs for the NK₁ receptors in rodents compared with other species.⁴ ARG studies are valuable for determination of NK₁ receptor distribution and the activity and species-selectivity of various SPAs. However, ARG studies are limited by the fact that the analyses can be performed only postmortem, which underscores the need for a methodology such as PET that permits examination of receptor distribution and occupancy *in vivo*.

PET STUDIES

In contrast to ARG, PET is a dynamic, minimally invasive imaging technique that can be used to assess blood flow, metabolic activity, drug distribution, or receptor binding in living subjects. PET displays images obtained from the decay of low-dose, high specific activity positron-emitting radionuclides that are incorporated into tracer molecules with high selectivity for specific receptors. PET is becoming increasingly popular as a research tool in the exploration of novel CNS drugs, as it is the leading *in vivo* receptor imaging technique available for

Figure 1. Distribution of Neurokinin-1 (NK₁) Receptors in the Human Brain, As Determined by Autoradiographic Studies Using [¹²⁵I]Substance P^a



^aAdapted from O'Donnell and Rigby¹⁴; Merck & Co., Inc., data on file. Abbreviation: PAG = periaqueductal gray.

use in human subjects. PET can therefore establish a unique bridge between the laboratory and the clinic by providing important pharmacokinetic and pharmacodynamic information (e.g., blood-brain barrier penetration, degree and duration of receptor occupancy) that can influence the choice of a drug candidate and optimize hypothesis testing. The use of PET to focus the proof-of-concept studies is particularly important for evaluation of novel CNS agents because useful surrogate endpoints are often lacking.

One such example has been the monitoring of 5-HT_{1A} autoreceptor expression in depressed and control patients.¹⁶ Previous postmortem studies of suicide victims and depressed subjects had implicated this receptor in the pathophysiology of major depression. Major depressive disorders are thought to be associated with decreased 5-HT transmission and alterations in the number of 5-HT receptors, including the 5-HT_{1A} autoreceptor.¹⁷ Using the radiolabeled 5-HT_{1A} antagonist [¹¹C]WAY-100635, PET studies demonstrated a significant reduction in 5-HT_{1A} binding in the midbrain raphe (by 41.5%; $p < .02$) and mesiotemporal cortex (by 26.8%; $p < .025$) in untreated de-

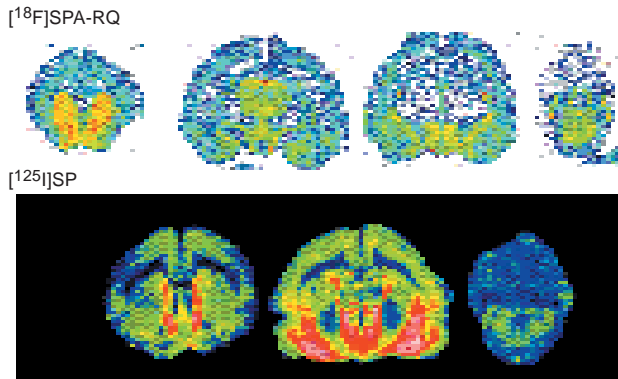
pressed patients (vs. the control subjects).¹⁶ Additionally, reduced [¹¹C]WAY-100635 binding was also noted in the occipital cortex and postcentral gyrus of depressed patients.¹⁶ A subsequent PET study, however, demonstrated that the widespread reduction in 5-HT_{1A} receptor binding among patients with depression was not reversed in response to successful antidepressant treatment with SSRIs,¹⁷ suggesting that it is not simply involved in disease pathogenesis or drug response.

Preclinical PET Studies of the SP-NK₁ Receptor System

The growing preclinical and clinical evidence implicating the SP-NK₁ receptor pathway in pathophysiology of depression and CINV, coupled with the successful use of PET in the studies of other neurotransmitter receptor systems, prompted the initiation of a program designed to discover an NK₁ receptor ligand that can be used for PET studies.

The radiolabeled NK₁ receptor ligand [¹⁸F]SPA-RQ is a selective high-affinity (0.04 nM) ligand that was

Figure 2. Comparison of the Autoradiographic Distribution of [^{18}F]SPA-RQ and [^{125}I]Substance P (SP) in the Guinea Pig Brain^a



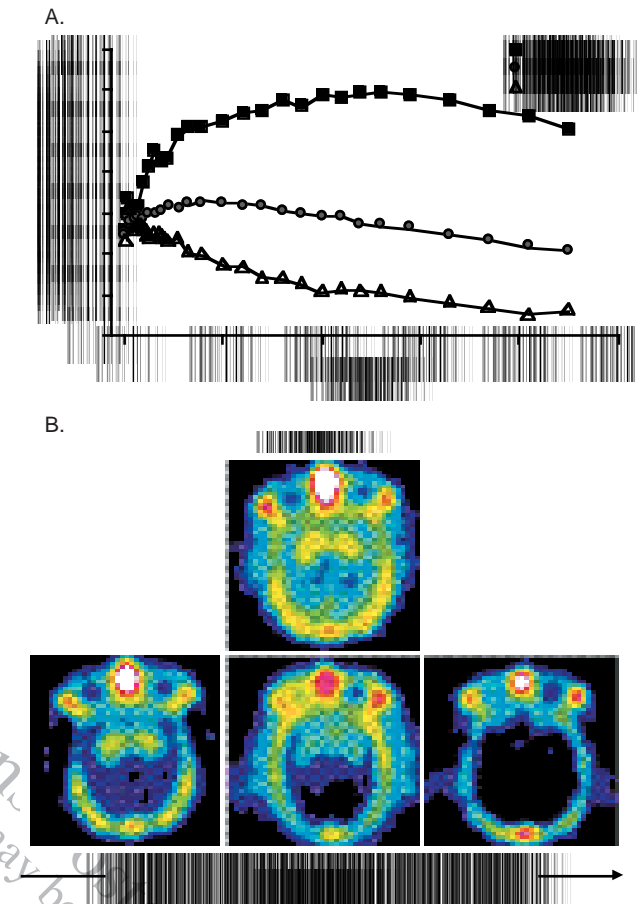
^aO. Solin; Merck & Co., Inc., Turku, Finland; data on file, 2002.

chosen over other candidates, such as [^{11}C]GR203040 and [^{11}C]GR205171,¹⁸ largely because of the longer half life of [^{18}F] (110 minutes vs. 20 minutes for carbon-labeled tracers), which enables a longer imaging time (up to 8 hours vs. 1.5 hours, respectively) and increases the probability that the tracer will reach an equilibrium between the blood and the brain. In guinea pig brain, [^{18}F]SPA-RQ demonstrated a high affinity for the NK₁ receptor, distribution identical to that of the endogenous NK₁ receptor ligand SP (Figure 2), an intense NK₁ receptor-specific binding signal with low nonspecific binding, and good blood-brain barrier penetration, thus fulfilling all the criteria for a useful PET tracer. Importantly, no specific [^{18}F]SPA-RQ binding was observed in the cerebellum, an area of the brain known from ARG [^{125}I]SP binding studies to lack NK₁ receptors, thereby defining a useful internal reference region for background, non-NK₁ receptor-specific accumulation of the tracer.

Subsequent experiments in rhesus monkeys sought to validate [^{18}F]SPA-RQ by evaluating its regional distribution and kinetics, in vitro with autoradiography on frozen brain sections and in vivo with PET neuroimaging. ARG studies revealed high binding of [^{18}F]SPA-RQ in areas known to be rich in NK₁ receptors, such as the hippocampus, putamen, and caudate, and no binding in the cerebellum (negative control). Binding in the putamen and caudate was abolished by preadministration of unlabeled SPA-RQ, confirming the selectivity of [^{18}F]SPA-RQ for the NK₁ receptor.

In order to assess the in vivo distribution of NK₁ receptors in the rhesus monkey brain and their occupancy by various SPAs, PET studies using [^{18}F]SPA-RQ tracer were performed before and after administration of various doses of SPAs (given as a 5-minute infusion), with an imaging time of 4 hours. At baseline, the highest [^{18}F]SPA-RQ activity was noted in the caudate, with significant accumulation also seen in the cortical gray (Figure 3A). In the cer-

Figure 3. (A) Time-Activity Curves of [^{18}F]SPA-RQ in Various Regions of the Rhesus Monkey Brain and (B) Positron Emission Tomography Images of the Rhesus Monkey Brain Using [^{18}F]SPA-RQ at Baseline and After Treatment With Increasing Doses of the Substance P Antagonist Aprepitant (MK-0869)^a



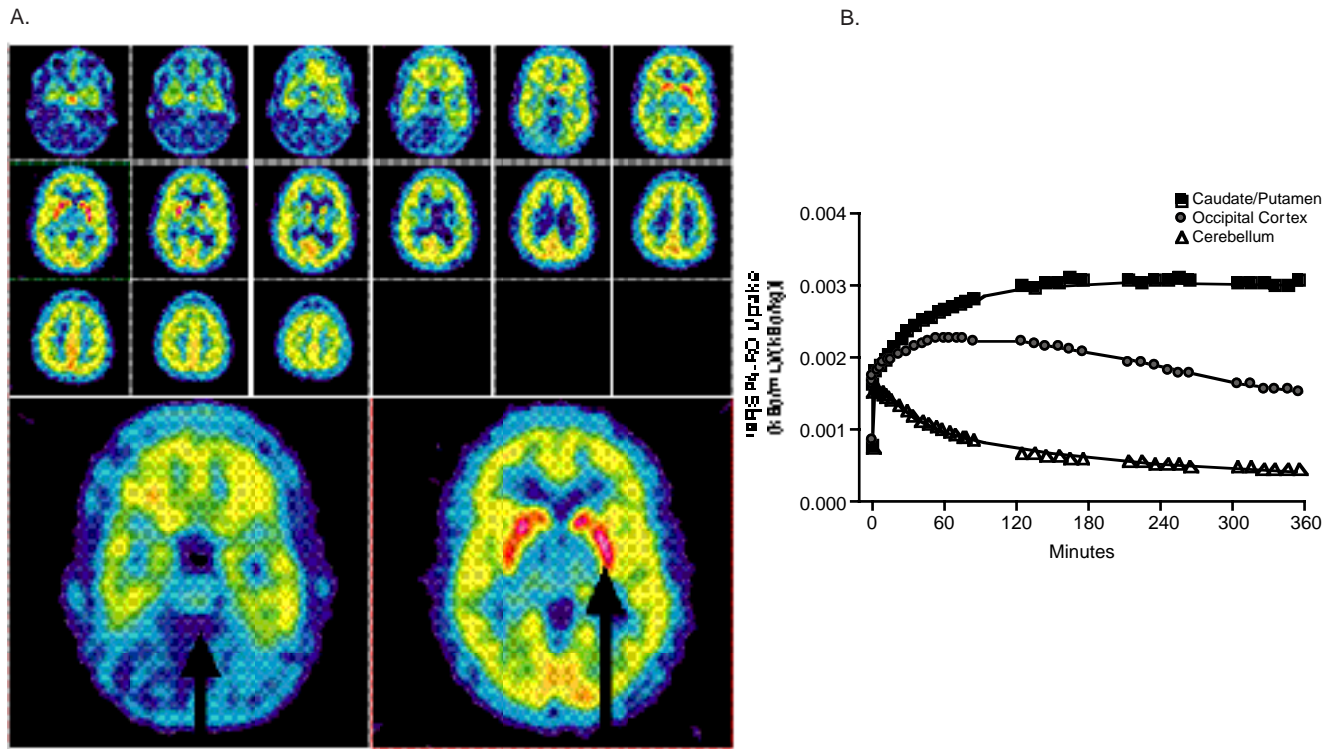
^aM. Bergstrom; Merck & Co., Inc., Uppsala, Sweden; data on file, 2002.

ebellum, the tracer penetrated the tissue, but then washed out with time. Pretreatment with increasing doses of the unlabeled SPA aprepitant decreased [^{18}F]SPA-RQ binding in the caudate and cortex (Figure 3B), whereas no such effect was observed in the cerebellum, where NK₁ receptors are absent. These results indicated the potential for PET studies with [^{18}F]SPA-RQ to help with the selection of lead compounds and dose optimization.

Clinical PET Studies of the SP-NK₁ Receptor System

Preclinical validation of [^{18}F]SPA-RQ led to additional experiments in the clinical setting. The distribution of NK₁ receptor in the normal human brain was studied by monitoring [^{18}F]SPA-RQ activity with 4 PET scans over a period of 6 hours. Arterial blood sampling was performed to determine the delivery of the tracer from plasma to brain at various times. The highest [^{18}F]SPA-RQ activity

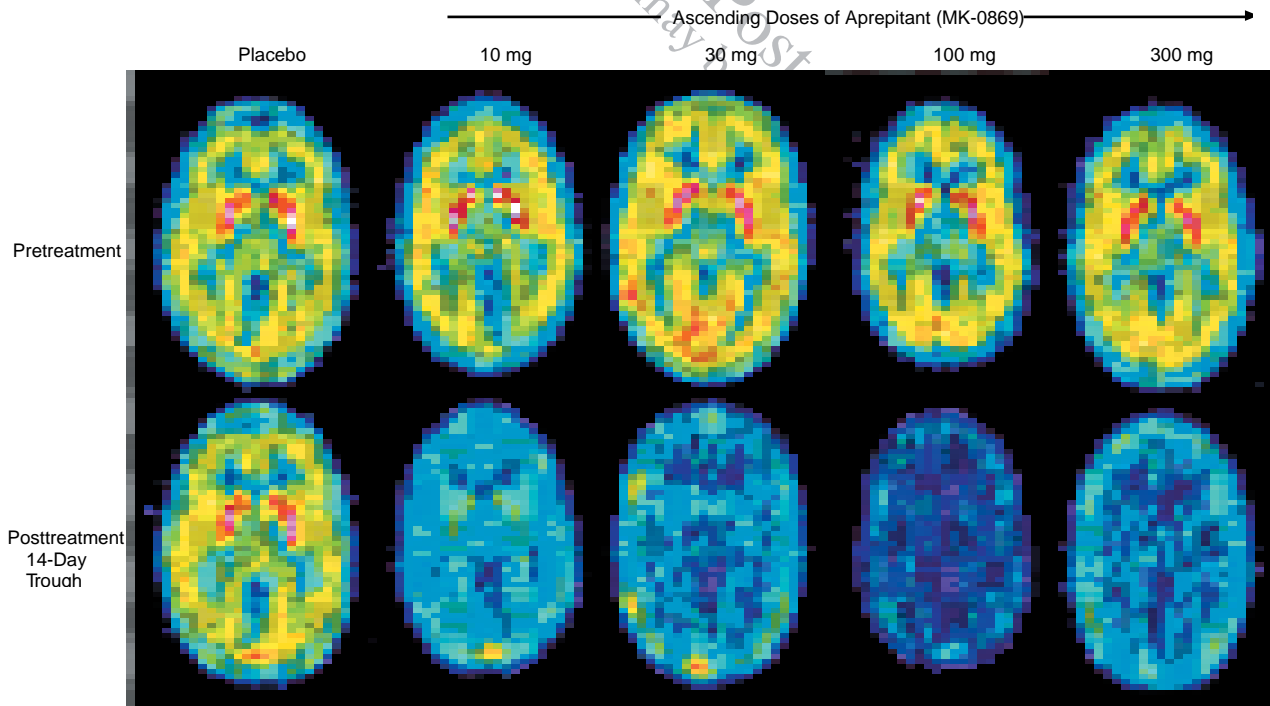
Figure 4. (A) Positron Emission Tomography Images of [¹⁸F]SPA-RQ Activity in Human Brain^a and (B) Time-Activity Curves of [¹⁸F]SPA-RQ Activity in the Human Caudate/Putamen, Occipital Cortex, and Cerebellum^b



Cerebellum: Low NK Receptor Expression Striatum: High NK Receptor Expression

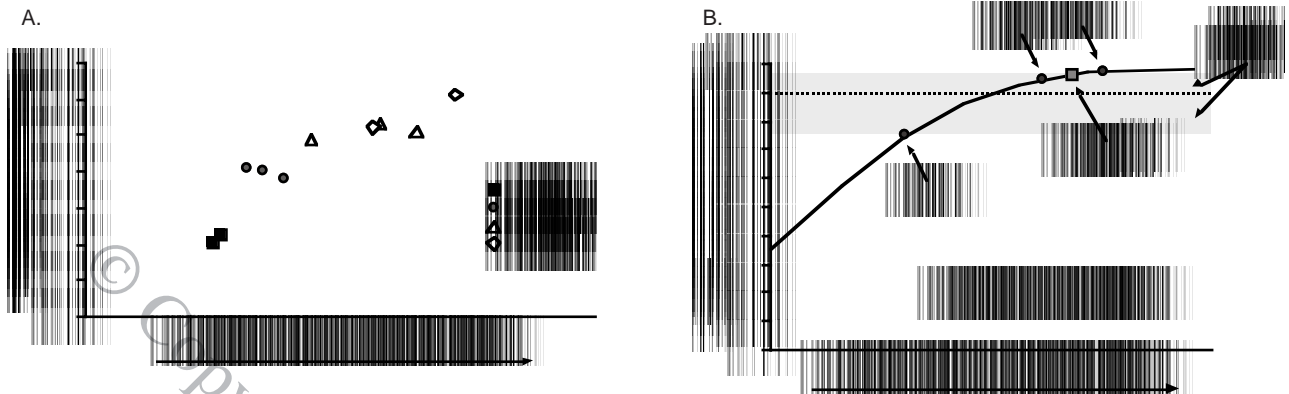
^aM. Bergstrom; Merck & Co., Inc., Uppsala, Sweden; data on file, 2002. ^bJ. Hietala; Merck & Co., Inc., Turku, Finland; data on file, 2002.

Figure 5. Positron Emission Tomography (PET) Images of the Human Brain Before and After 14-Day Treatment With Placebo or the Substance P Antagonist Aprepitant (MK-0869; 10 mg, 30 mg, 100 mg, and 300 mg) Using [¹⁸F]SPA-RQ Tracer^a



^aM. Bergstrom; Merck & Co., Inc., Uppsala, Sweden; data on file, 2002.

Figure 6. (A) Relationship Between Plasma Levels and Occupancy of Neurokinin-1 (NK₁) Receptors by the Substance P Antagonist Aprepitant (MK-0869), as Determined by Positron Emission Tomography (PET) Studies With [¹⁸F]SPA-RQ, and (B) Projected Occupancy of NK₁ Receptors by Aprepitant Doses Used in the Clinical Trials Involving Patients With Depression and Chemotherapy-Induced Nausea and Vomiting (CINV)^a



^aM. Bergstrom; Merck & Co., Inc., Uppsala, Sweden; data on file, 2002. ^bSee Kramer et al.¹¹ ^cSee Chawla et al.¹⁹

was found in brain regions with a high NK₁ receptor density, such as striatum, putamen, caudate, and brain stem (Figure 4A). The tracer activity in the caudate and putamen increased continuously during the first 2 hours and then remained at this level for the entire 6-hour duration of imaging (Figure 4B). Uptake of [¹⁸F]SPA-RQ into the cerebellum was rapid, but the tracer washed out readily, consistent with the lack of NK₁ receptors in this brain region (Figure 4B).

The next phase of the PET studies examined the relationship between dose, plasma concentration, and NK₁ receptor occupancy using the SPA aprepitant. The goal of these studies was to provide a framework for prediction of NK₁ receptor occupancy required to achieve optimal therapeutic effect in treatment of CINV and depression. At a dose of 300 mg/day, aprepitant improves symptoms of depression to a similar extent as the SSRI paroxetine (20 mg/day).¹¹ In the treatment of patients who developed CINV in response to treatment with cisplatin, an initial daily dose of 40 mg of aprepitant followed by 25-mg daily doses showed some efficacy, but a higher dosing regimen (initial dose of 125 mg, followed by subsequent daily doses of 80 mg) was considerably more effective.¹⁹ No further efficacy improvements over the 125-mg/80-mg aprepitant regimen were observed with the highest dose (initial dose of 375 mg, followed by 125-mg daily dose).¹⁹ Plasma concentrations of aprepitant were measured in patients enrolled in the depression trials and in healthy volunteers treated with the dosing regimens used in the CINV study. This provided the opportunity to assess the approximate level of occupancy of central NK₁ receptors achieved by the doses of aprepitant used in these successful trials.

The distribution of NK₁ receptors in the CNS of healthy male volunteers was evaluated using [¹⁸F]SPA-RQ prior to and after 14-day treatment with placebo or increasing doses of aprepitant (10–300 mg); regions of interest were

the NK₁ receptor-dense striatum and the NK₁ receptor-devoid cerebellum. The choice of striatum was based on the observation that this region shows the most intense [¹⁸F]SPA-RQ activity and thus provides the greatest opportunity for assessment of NK₁ receptor blockade. In agreement with previous results, the striatum and cerebellum had high and low [¹⁸F]SPA-RQ activities, respectively, before the treatment was initiated (Figure 5). After treatment, a dose-proportional reduction in tracer binding to NK₁ receptors in the striatum was observed with aprepitant, but not with placebo (Figure 5). It is noteworthy that [¹⁸F]SPA-RQ binding in other regions of the brain known to express NK₁ receptors (e.g., amygdala) was also reduced, in line with observations made in the striatum. On the basis of these findings, a plasma concentration vs. receptor occupancy relationship was established (Figure 6A). The data suggest that a trough concentration following treatment with the 10-mg dose of aprepitant corresponds to approximately 60% receptor occupancy, whereas the occupancy of ≥ 90% of NK₁ receptors requires aprepitant doses ≥ 100 mg. Curve fitting to the plasma concentration–receptor occupancy curves showed that high levels of NK₁ receptor occupancy were associated with significant antidepressant effects and optimal activity against CINV. Both the 300-mg dose of aprepitant used in the treatment of depression and the initial 125-mg dose studied for treatment of emesis blocked ≥ 90% of NK₁ receptors in the CNS (Figure 6B), whereas the initial 40-mg dose used in the study of emesis resulted in lower (75%) receptor occupancy (Figure 6B). Interestingly, this analysis also illustrates why a 375-mg dose of aprepitant had no advantage over the 125-mg dose in the treatment of CINV,¹⁹ since the NK₁ receptor occupancies achieved by these doses were essentially the same.

The [¹⁸F]SPA-RQ PET data were also of value in addressing the apparent inactivity of aprepitant in proof-

of-concept studies for the alleviation of somatic pain. The results of the PET studies indicate that high levels of central NK₁ receptor occupancy were likely to have been achieved with aprepitant doses used in the clinical pain trials.⁴ This suggests that the absence of activity of aprepitant in the modulation of pain responses is not a result of inadequate blockade of NK₁ receptors, but rather an indication that the SP-NK₁ receptor pathway is not directly involved in the pain conditions studied to date.

CONCLUSIONS

Preclinical and clinical studies suggest that [¹⁸F]SPA-RQ represents a valuable tracer for PET imaging of NK₁ receptors in the CNS. Preclinical studies showed that [¹⁸F]SPA-RQ has a high affinity for the NK₁ receptor, distribution identical to that of the endogenous NK₁ receptor ligand SP, low nonspecific binding, and good blood-brain barrier penetration, thus fulfilling the criteria of a useful PET tracer. Subsequent experiments in rhesus monkeys and humans confirmed the high selectivity of [¹⁸F]SPA-RQ for the NK₁ receptor and its usefulness in the quantification of NK₁ receptor occupancy with various doses of SPAs. Furthermore, these studies have helped to identify the degree of receptor occupancy that is required to achieve consistent clinical benefits in the treatment of depression and CINV. This tracer may also be useful for monitoring of NK₁ receptor occupancy in patients with depression, as well as for examining the effects of currently available antidepressants on the activity of the SP-NK₁ receptor pathway.

Drug names: cisplatin (Platinol and others), fluoxetine (Prozac and others), paroxetine (Paxil).

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