[2-[^{18}F]Fluoromethoxy-5-(5-trifluoromethyl-tetrazol-1-yl)-benzyl]([2*S*,3*S*]2-phenyl-piperidin-3-yl)-amine

[^{18}F]SPA-RQ

The MICAD Research Team

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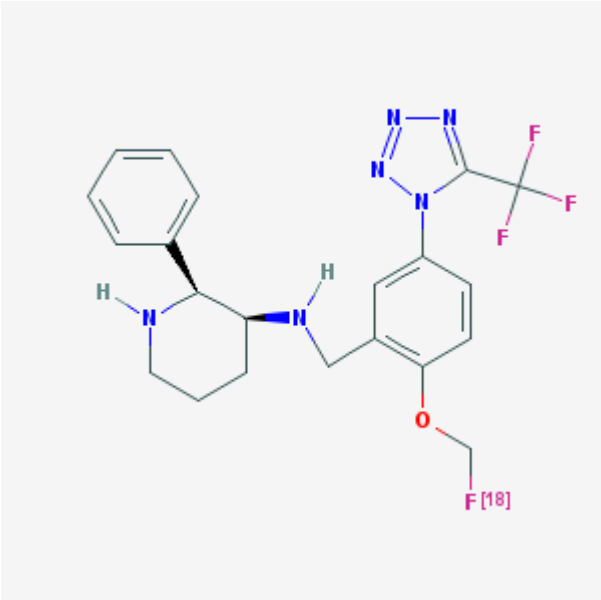
Chemical name:	[2-[^{18}F]Fluoromethoxy-5-(5-trifluoromethyl-tetrazol-1-yl)-benzyl]([2*S*,3*S*]2-phenyl-piperidin-3-yl)-amine
Abbreviated name:	[^{18}F]SPA-RQ
Synonym:	[^{18}F]Substance-P antagonist-Receptor quantifier[^{18}F]L-829
Agent Category:	Compound
Target:	NK_1 receptor
Target Category:	Receptor binding
Method of detection:	PET
Source of signal:	^{18}F
Activation:	No
Studies:	• *In vitro* • Other non-primate mammals • Non-human primates • Humans



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Background

[PubMed]

[2-[^{18}F]Fluoromethoxy-5-(5-trifluoromethyl-tetrazol-1-yl)-benzyl]([2*S*,3*S*]2-phenyl-piperidin-3-yl)-amine ([^{18}F]SPA-RQ) is a radioligand developed for positron emission tomography (PET) imaging of NK_1 receptors (SP receptors) in the central nervous system (CNS) (1).

Tachykinins are 10-12 amino acid peptides that share a common carboxy-terminal sequence "Phe-X-Gly-Leu-Met-amide" where "X" is different but always a hydrophobic residue that is either an aromatic or a beta-branched aliphatic (2-4). This peptide family consists of substance P (SP), neurokinin A (NK_A), and neurokinin B (NK_B). The tachykinin peptides mediate their effects by specific G protein coupled receptors. These receptors are divided into three subtypes: neurokinin 1 (NK_1, formerly the SP receptor), neurokinin 2 (NK_2, formerly the substance K/substance E receptor/NK-A receptor), and neurokinin 3 (NK_3, formerly the NK-B receptor) receptors. The effects of SP are mediated primarily via the NK_1 receptor subtypes. There is evidence that SP behaves like a neurotransmitter involved in regulation of emotional and behavioral responses to a range of noxious and stressful stimuli (5). SP may also play a role in neurogenic inflammation, vasomotor control, and many gastrointestinal functions. Studies have shown that in the brain SP is found throughout the neocortex, in limbic areas, habenula, periaqueductal gray, midbrain nuclei, and especially enriched in the basal ganglia. There is little SP in the cerebellum. The distribution of the NK_1 receptors in the brain generally corresponds to that of SP.

SP-NK_1 receptor pathways are found in both CNS and peripheral nervous system. The CNS pathways have been implicated in the pathophysiology of pain, nausea/emesis, and depression disorders (6). PET and single-photon emission tomography of radioligands targeting NK_1 receptors can visualize and study the CNS NK_1 receptors in normal and pathologic states. These studies can identify the degree of receptor occupancy in patients with depression and the change in response to therapy (6). A number of NK_1 selective agonists and antagonists have been successfully labeled, but they failed to provide a specific signal *in vivo* (1, 6). Solin et al (1). developed a selective NK_1 receptor antagonist, SPA-RQ, with a high affinity for NK_1 receptor (IC_{50} = 67 pM) and moderate lipophilicity (logP = 1.8).

Synthesis

[PubMed]

Solin et al. (1) reported the synthesis and characterization of [^{18}F]SPA-RQ. The precursors were prepared either as [2-hydroxy-5-(5-trifluoromethyl-tetrazol-1-yl)-benzyl]

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([2*S*,3*S*]2-phenyl-piperidin-3-yl)-amine hydrochloride or (2*S*,3*S*)-1-t-butoxycarbonyl-2-phenyl-3-[2-hydroxy-5-(5'-rifluoromethyltetrzol-1-yl)phenylmethyleneamino]piperidine. The first precursor gave very low and unreliable yields. The second precursor with a tert-butoxycarbonyl (t-BOC) protecting group was prepared from 2-hydroxy-5-(5-trifluoromethyl-tetrazol-1-yl)-benzaldehyde in two steps. In a five-step method of radiosynthesis, [^{18}F]FCH_2Br was first synthesized from dibromomethane via a nucleophilic substitution with [^{18}F]F–. [^{18}F]F– was obtained from the nuclear reaction $^{18}O(p,n)^{18}F$, and the target water was removed by azeotropic distillations. Dibromomethane in acetonitrile was added to produce [^{18}F]FCH_2Br with about 40% yield (decay corrected to the end of bombardment). [^{18}F]FCH_2Br was used to [^{18}F]fluoroalkylate the deprotonated phenolic hydroxyl group of the precursor by bubbling through the precursor solution in dimethylformamide (DMF) and cesium carbonate. The reaction mixture was heated at 110 °C for 8 min. After DMF was removed, trifluoroacetic acid was added for a 2-min hydrolysis at room temperature to cleave the t-BOC protecting group. The resulting [^{18}F]SPA-RQ was purified by preparative high performance liquid chromatography. The radiochemical yield was 9.6 ± 4.0% (n = 111), and the radiochemical purity was 99.5 ± 0.2%. The specific activity was 1190 ± 1310 GBq (32 ± 35.4 Ci)/μmol at the end of synthesis. The total synthesis time was about 60 min.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

Hietala et al. (2) conducted postmortem human brain receptor autoradiography with [^{18}F]SPA-RQ by incubating three left cerebral hemispheres with 50 pM [^{18}F]SPA-RQ (specific activity ≥ 400 GBq (10.8 Ci)/μmol) for 60 min at room temperature. Nonspecific binding was estimated by competing the radiotracer binding with 1 mM excess of an unlabeled specific high-affinity NK_1 receptor antagonist (GR203040). The relative radioactivity concentrations were highest in striatum > cortical regions = thalamus > cerebellum. The addition of GR203040 prevented radioactivity localization almost completely in caudate, putamen, and occipital cortical areas with %blockade of 98 ± 2, 94 ± 2, and 95 ± 4, respectively. The cerebellar radioactivity level was not affected by GR203040 because there was minimal NK_1 receptor present.

Animal Studies

Rodents

[PubMed]

No publication is currently available.

Other Non-Primate Mammals

[PubMed]

Solin et al. (1) injected [^{18}F]SPA-RQ into 4 guinea pigs. Two animals (animal 3 and 4) were pretreated with a NK_1 selective antagonist (2 mg/kg) 2 min before the administration. The animals were sacrificed at 180 min after injection, and brains were removed for assay. The radiotracer showed a high radioactivity localization in the caudate/putamen, moderate radioactivity in the cortex, and low radioactivity in the cerebellum. For the untreated animals, animal 1 and 2, the ratios of caudate/putamen were 14 and 7.1, respectively. Their ratios of cortex to cerebellum were 4.7 and 2.7, respectively. In comparison, these cortex/cerebellum ratios in the pretreated animal 3 and 4 were ranging from 1.0 to 1.3.

Non-Human Primates

[PubMed]

Hargreaves (6) reported that the highest [^{18}F]SPA-RQ radioactivity concentration was in the caudate of the monkey brain. In the cerebellum, the radioactivity was washed out with time. Pretreatment with an unlabeled SP antagonist decreased ^{18}F]SPA-RQ radioactivity in the caudate and cortex, but no effect was observed in the cerebellum.

Human Studies

[PubMed]

PET imaging with [^{18}F]SPA-RQ was performed in 10 healthy male volunteers (2). Each subject received i.v. 125-135 MBq (3.38-3.65 mCi) of [^{18}F]SPA-RQ (average specific activity = 1,995 GBq (53.9 Ci)/μmol; 114 ng). There was a rapid radioactivity localization in the brain with the highest radioactivity levels in the putamen and caudate nucleus. The cerebellum level was the lowest as the radioactivity was washed out readily. The neocortex and thalamus radioactivity levels were between the striatal level and cerebellar level. The highest putamen/cerebellum and caudate/cerebellum ratios were between 5 and 6 at 215 min and 225 min, respectively. Based on the reference tissue input model, the NK_1 binding potentials (n = 4) were 5.24 ± 0.40 (caudate), 5.72 ± 0.33 (putamen), 2.60 ± 0.60 (ventral midbrain), 2.60 ± 0.54 (posterior cingulated cortex), and 2.60 ± 0.13 (amygdala). The distribution of [^{18}F]SPA-RQ *in vivo* was similar to the *in vitro* pattern reported in human brain receptor autoradiography studies. The study suggested that NK_1 receptors were widely distributed throughout the human brain with highest density in the striatum and visual cortex. Plasma radioactivity analysis by planar chromatography and digital autoradiography indicated that about 30-40% of [^{18}F]SPA-RQ remained unchanged at 80 min. Unidentified hydrophilic metabolites and free fluoride were found in these plasma samples.

References

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