[^{11}C]*N*,*N*-Dimethyl-2-(2-amino-4-cyanophenylthio)benzylamine

[^{11}C]DASB

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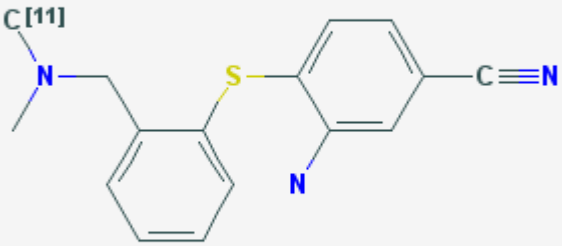
Chemical name:	[^{11}C]*N*,*N*-Dimethyl-2-(2-amino-4-cyanophenylthio)benzylamine
Abbreviated name:	[^{11}C]DASB
Synonym:	[^{11}C]3-Amino-4-(2-dimethylaminomethylphenylsulfanyl)-benzonitrile
Agent Category:	Compound
Target:	Serotonin transporter
Target Category:	Serotonin transporter binding
Method of detection:	PET
Source of signal \contrast:	^{11}C
Activation:	No
Studies:	• *In vitro* • Rodents • Non-primate non-rodent mammals • Non-human primates • Humans



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Background

[PubMed]

Serotonin (5-hydroxytryptamine, 5-HT) has diverse physiological roles as a neurotransmitter in the central nervous system (1). It also is a regulator of smooth muscle function and platelet aggregation. The brain 5-HT system has been implicated in several neuropsychiatric disorders, including major depression, anxiety, obsessive-compulsive disorder, and schizophrenia (2, 3). The serotonergic transmission is controlled in part by the serotonin transporter (SERT), which regulates the concentration of free, active 5-HT in the synaptic cleft. Citalopram, paroxetine, and fluoxetine were developed as selective SERT inhibitors to treat depression and anxiety disorders by blocking the reuptake of 5-HT [PubMed]. The blockade led to a higher 5-HT concentration in the synaptic cleft, and subsequently an improved well-being of the patients.

Trans-1,2,3,5,6,10-β-Hexahydro-6-[4-([^{11}C]methylthio)phenyl[pyrrolo-[2,1-a]isoquinoline ([^{11}C]McN5652) binds selectively to the SERT, and its regional distribution of binding in humans correlates well with the known distribution of the SERT in human brain (4). However, usefulness of [^{11}C]McN5652 may be limited by its nonspecific binding and slow release from specific binding sites (5). [^{11}C]*N*,*N*-Dimethyl-2-(2-amino-4-cyanophenylthio)benzylamine ([^{11}C]DASB) was found to be a promising tracer for SERT imaging in animals and humans (6-9). It displayed a nanomolar affinity for SERT and a greater than 1000-fold affinity for SERT over dopamine transporter (DAT) and norepinephrine transporter (NET). The uptake in the SERT-rich brain regions was both saturable and selective for SERT.

Synthesis

[PubMed]

[^{11}C]DASB was synthesized by alkylation of its *N*-normethyl precursor using [^{11}C]iodomethane in 30-55% radiochemical yield (not corrected for decay) in 25-30 min (6). Chemical and radiochemical purities were >98% with specific activities of 25-55 GBq/μmol (0.68-1.49 Ci/μmol) at the end of synthesis.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

[^{11}C]DASB was reported to bind specifically to the serotonergic transporter in homogenates of rat forebrain membrane (8). The transporter-binding affinity of DASB was evaluated by competitive radioaffinity assays for serotonin (SERT), norepinephrine (NET), and dopamine (DAT). Binding affinity (K_i, nM) of DASB at SERT, NET, and DAT were 0.97, 6,000, and 1,180 nM, respectively. DASB binding selectively to SERT over other monoamine transporters was also reported previously using cloned human transporters (6). DASB inhibited selectively [^{3}H]5-HT re-uptake into rat brain synaptic vesicles. K_d,

obtained from saturation data, was 0.54 nM, and B_{max} was 1.4 pmol/mg protein (10). The IC_{50} of serotonin to displace 50% of binding of 1.0 nM [11C]DASB was 3.47 μM.

Animal Studies

Rodents

[PubMed]

Intravenous injection of [11C]DASB in rats resulted in high uptake of radioactivity in the lungs (5.99% injected dose (ID/g)) and kidneys (2.62% ID/g) at 5 min after injection (8). Less pronounced uptake was seen in the whole brain (0.79% ID/g). The uptake in the hypothalamus (0.8% ID/g), thalamus (0.64% ID/g), hippocampus (0.5% ID/g), striatum (0.55% ID/g), and cortex (0.5% ID/g) was higher than the cerebellum (0.13% ID/g) at 45 min (6). The brain regional radioactivity was blocked by pretreatment of paroxetine and fluoxetine (SERT inhibitors), except in the cerebellum, indicating that SERT is low and the cerebellum can be used as a reference region (8). The [11C]DASB uptake in the SERT-rich brain regions returned to >90% baseline levels in 24-48 h after paroxetine treatment. Pretreatment of rats with unlabeled DASB reduced binding of [11C]DASB in a dose-dependent manner. The mean ED_{50} for the whole brain is 56 nmol/kg. Elimination of [11C]DASB was via the hepatobiliary and renal systems.

Other Non-Primate Mammals

[PubMed]

[11C]DASB (200 MBq or 5.4 mCi) was injected in pigs to study its positron emission tomography (PET) imaging properties of brain SERT (11). The fraction of intact tracer in plasma at 10 min after injection was 35%. Citalopram pretreatment reduced the binding potential and distribution volume of [11C]DASB markedly in the mesencephalon, striatum, and frontal cortex. There was substantial agreement between results of several methods of kinetic analysis. There was a uniform displacement of 80% of [11C]DASB specific binding after citalopram *in vivo*.

Non-Human Primates

[PubMed]

In monkeys, [11C]DASB uptake was greatest in lungs, followed by the urinary bladder, gallbladder, brain, and other organs at 7-95 min (12). The tracer was eliminated via the hepatobiliary and renal systems. Paroxetine (SERT inhibitor) and 3,4-methylenedioxymethamphetamine (5-HT neurotoxicity) reduced the uptake of [11C]DASB in brain regions with high SERT density (13). The biological half-life in plasma was 30 min. The metabolism led to very polar metabolites (19% of total [11C]DASB radioactivity in 30 min) and one or more lipophilic metabolites in the plasma.

Human Studies

[PubMed]

Nine healthy volunteers received intravenous injections of 350 MBq (9.7 mCi) [^{11}C]DASB (7). Sequential images of the brain were taken over a 90-min period. The highest uptake was in the mid-brain, thalamus, hypothalamus, and striatum. The peak uptake occurred at 30-40 min. After pretreatment with an oral dose of 40 mg of citalopram, there was an 80% reduction in specific binding of [^{11}C]DASB in SERT-rich regions. The metabolism of [^{11}C]DASB was rapid, with about 50% of the intact compound remaining in plasma at 20 min after injection.

No difference in regional SERT binding potential was found between major depressive episodes and normal subjects as measured by [^{11}C]DASB PET (9). In a subgroup of patients with major depressive episodes patients and with more negativistic dysfunctional attitudes, there was a significantly higher SERT binding potential, which led to low extracellular 5-HT. It was suggested that the lower 5-HT level caused these patients to feel more negativistic. [^{11}C]DASB PET is being evaluated as a useful tool for antidepressant development (14), obsessive-compulsive disorder studies (15) and alcoholism (16).

Human dosimetry of [^{11}C]DASB was estimated in seven normal volunteers (17). Dynamic whole-body PET scans were acquired after the injection of 669 ± 97 MBq (18.1 ± 2.6 mCi) of [^{11}C]DASB. Uptake of [^{11}C]DASB in the lungs was rapid and high, with a peak of 53.1%ID within 18-46 s after injection. About 12% ID was excreted in urine. The organs that received the highest absorbed doses were found to be the lungs (0.0328 mGy/MBq or 121 mrad/mCi), the urinary bladder (0.012 mGy/MBq or 44 mrad/mCi), the kidneys (0.0093 mGy/MBq or 34 mrad/mCi), the gallbladder (0.0093 mGy/MBq or 34 mrad/mCi), and the liver (0.0064 mGy/MBq or 24 mrad/mCi). The effective dose was calculated as 0.0070 mSv/MBq (26 mrem/mCi) for a 70-kg-standard man.

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