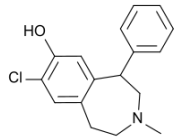
SCH 23390

SCH 23390 is a synthetic compound that acts as a selective, high-affinity antagonist of D_1 receptors. It is widely used in scientific research to investigate the function of the D_1 receptor.

Chemical Name: 7-chloro-3-methyl-1-phenyl-1,2,4,5-tetrahydro-3-benzazepin-8-ol
Formula: $C_{17}H_{18}ClNO$



Molecular Mass: 287.78 g/mol
Availability: Schering plough

Biodistribution

Biodistribution studies in mice showed a high accumulation of radioactivity in the intestines, followed by the liver, kidney, lung, and brain (0.17% ID/g) at 60 min after injection of [^{11}C]SCH 23390. There was a rapid accumulation of the tracer in the striata within the first ten min (4.88% ID/g), followed by a slow decrease of radioactivity to 2.25% ID/g at 60 min. In contrast, radioactivity in the cerebellum decreased continuously from 1 min (3.10% ID/g) to 60 min (0.10% ID/g). The striatum-to-cerebellum ratios were 1.3 and 23.4 at 1 and 60 min, respectively.	Leung K. (R)-(+)-8-Chloro-2,3,4,5-tetrahydro-3-[11C]methyl-5-phenyl-1H-3-benzazepin-7-ol([11C]SCH 23390). Molecular Imaging and Contrast Agent Database (MICAD) [Internet]. Bethesda (MD): National Center for Biotechnology Information (US); 2004-2011. 2005 Nov 22 [updated 2012 Jan 16]. PMID: 20641454
Two positron-emitting analogues of SCH 23390, one labelled with 75Br (or 76Br) and another with 11C, were evaluated in mice in vivo as potential PET tracers for central dopamine D1 receptors. Results show that indeed cerebral uptake was consistent with dopamine receptor innervation. Because of the relatively rapid pharmacokinetics of this drug, 11C-labelled SCH 23390 would be best suited for PET imaging.	DeJesus OT, Van Moffaert GJ, Friedman AM. Evaluation of positron-emitting SCH 23390 analogs as tracers for CNS dopamine D1 receptors. Int J Rad Appl Instrum B.1989;16(1):47-50.

Receptor Affinity

SCH 23390 was reported to have selective binding affinity to D_1 (striatum) and 5-HT_{2A} (frontal cortex) receptor sites in homogenates of rat brain membranes. The K_i values for D_1 ([^{3}H]piflutixol), D_2 ([^{3}H]spiroperidol) in the striatal membranes and 5-HT_{2A} ([^{3}H]spiroperidol) in the cortical membranes were 1.3 nM, 880 nM and 30 nM, respectively. It has a K_i value of 690 nM for the α_1-adrenergic receptor in rat forebrain membrane.	Hyttel J. *SCH 23390 - the first selective dopamine D-1 antagonist.* Eur J Pharmacol. 1983;91(1):153–4.
The K_d value of [^{3}H]SCH 23390 was 0.53 nM for D_1 in rat striatum. The B_{max} value of [^{3}H]SCH 23390 for D_1 was 69 pmol/g tissue.	Billard W., Ruperto V., Crosby G., Iorio L.C., Barnett A. *Characterization of the binding of 3H-SCH 23390, a selective D-1 receptor antagonist ligand, in rat striatum.* Life Sci. 1984;35(18):1885–93.
SCH 23390 was used to study the role of the D-1 dopamine receptor in mediating the pre- and postsynaptic effects of dopamine agonists in the basal ganglia. Results suggested that	Carlson JH, Bergstrom DA, Walters JR. Neurophysiological evidence that D-1 dopamine receptor blockade attenuates postsynaptic but not autoreceptor-mediated

D-1 receptor blockade attenuates the postsynaptic, but not autoreceptor-mediated effects of dopamine agonists.	effects of dopamine agonists. Eur J Pharmacol. 1986 Apr 16;123(2):237-51. Review.
Using human putamen homogenates, the K_d values of [^{3}H]SCH 23390 and [^{3}H]raclopride, a D_2 antagonist, were 1.6 ± 0.22 nM (1.1 ± 0.38 nM with 40 nM ketanserin, a 5-HT_{2A} antagonist) and 2.0 ± 0.2 nM, respectively.	Hall H., Farde L., Sedvall G. *Human dopamine receptor subtypes--in vitro binding analysis using 3H-SCH 23390 and 3H-raclopride.* J Neural Transm. 1988;73(1):7–21.
SCH 23390 was found to have marginal effect on D_2, α_1-adrenergic, muscarinic and histaminergic receptors and only a slight effect on 5-HT_{2A} receptors	Hyttel J., Arnt J., van den Berghe M. *Selective dopamine D1 and D2 receptor antagonists.* Psychopharmacol Ser. 1989;7:109–22.
The affinity for the 5-HT_{2A} receptor is about 10-fold lower than that for the D_1 receptor, suggesting that specific [^{11}C]SCH 23390 binding visualized by PET represents mainly binding to D_1 receptors. However, unlike SCH 39166, SCH 23390 does have significant affinity at 5-HT2 receptors	M.E. Alburges, M.E. Hunt, R.D. McQuade, J.K. Wamsley D1-receptor antagonists: comparison of [3H]SCH39166 to [3H]SCH23390 J Chem Neuroanat, 5 (5) (1992), pp. 357–366 L.A. Taylor, C.E. Tedford, R.D. McQuade The binding of SCH 39166 and SCH 23390 to 5-HT1C receptors in porcine choroid plexus. Life Sci, 49 (20) (1991), pp. 1505–1511
[^{11}C]SCH 23390 PET studies of D_1 receptor distribution in healthy human brain were reported, showing a major localization of radioactivity in the striatum.	Chan G.L., Holden J.E., Stoessl A.J., Doudet D.J., Wang Y., Dobko T., Morrison K.S., Huser J.M., English C., Legg B., Schulzer M., Calne D.B., Ruth T.J. *Reproducibility of the distribution of carbon-11-SCH 23390, a dopamine D1 receptor tracer, in normal subjects.* J Nucl Med. 1998;39(5):792–7. [Hirvonen J., Nagren K., Kajander J., Hietala J. *Measurement of cortical dopamine d1 receptor binding with 11C[SCH23390]: a test-retest analysis.* J Cereb Blood Flow Metab. 2001;21(10):1146–50.
With Age	
B_{max} and K_d of dopamine D_1 receptor in striatum was estimated in rats of different ages (from 3.5 to 25 months) using [^{3}H]SCH 23390. There was a 30% decrease in the density of D_1 receptor in 25 months whereas, the K_d values remained constant.	Hyttel J. *Parallel decrease in the density of dopamine D1 and D2 receptors in corpus striatum of rats from 3 to 25 months of age.* Pharmacol Toxicol. 1989;64(1):55–7.
The binding potential (B_{max}/K_d) of [^{11}C]SCH 23390 as measured by PET in the rat striata decreased as a function of age by a maximum of 26%,	Suzuki M., Hatano K., Sakiyama Y., Kawasumi Y., Kato T., Ito K. *Age-related changes of dopamine D1-like and D2-like receptor binding in the F344/N rat striatum revealed by positron emission tomography and in vitro receptor autoradiography.* Synapse. 2001;41(4):285–93.
The binding potential of the D_1 receptors in the striatum and frontal cortex decreased with age by 35% and 39%, respectively in 17 healthy male subjects in age from 20 to 72 years old as visualized by PET	Suhara T., Fukuda H., Inoue O., Itoh T Suzuki K., Yamasaki T., Tateno Y. *Age-related changes in human D1 dopamine receptors measured by positron emission tomography.* Psychopharmacology (Berl). 1991;103(1):41–5.
There was an age dependent decrease of D_1 receptor binding potential in the caudate (6.9%), putamen (7.4%), and occipital cortex (8.6%) per decade in a PET study with 8 men and 10 women (22-74 years old). There was no difference in D_1 binding potentials between men and women.	Wang Y., Chan G.L., Holden J.E., Dobko T., Mak E., Schulzer M., Huser J.M., Snow B.J., Ruth T.J., Calne D.B., Stoessl A.J. *Age-dependent decline of dopamine D1 receptors in human brain: a PET study.* Synapse. 1998;30(1):56–61.
Dopamine D1 receptor binding in the cerebral cortex and striatum of 12 adolescents and 18 young adults was examined using [^{11}C]SCH 23390 PET. Over the age span of 10-30 years [^{11}C]SCH 23390 binding declined in all brain regions. Most pronounced decline in binding potential was observed in the cortical regions during adolescence.	Jucaite A, Forssberg H, Karlsson P, Halldin C, Farde L. Age-related reduction in dopamine D1 receptors in the human brain: from late childhood to adulthood, a positron emission tomography study. Neuroscience. 2010 Apr 28;167(1):104-10.
Marked age-related D1 receptor losses in striatal, limbic, and	Rieckmann A, Karlsson S, Karlsson P,

cortical areas were observed when compared in younger and elderly adults using [^{11}C]SCH 23390 PET. These results suggest that D1 receptor densities in different pathways are not regulated independently in younger adults, but segregate in older age, and that this segregation of D1 receptor systems may be related to age-related cognitive slowing.	Brehmer Y, Fischer H, Farde L, Nyberg L, Bäckman L. Dopamine D1 receptor associations within and between dopaminergic pathways in younger and elderly adults: links to cognitive performance. Cereb Cortex. 2011 Sep;21(9):2023-32. Epub 2011 Jan 21. PubMed PMID: 21258043.

Cognition

Recent research indicates a pattern of 'global influence' of dopamine on cognitive functioning. Dopamine D1 receptors in prefrontal cortex may be particularly important to higher-order cognitive functions but only a few investigations have addressed the D1–cognition link in healthy samples

An inverted U-shaped relation between prefrontal D1 receptor binding and Wisconsin Card Sorting Test performance was observed using PET in healthy subjects. D1 receptor binding in the dorsolateral prefrontal cortex was 'curvilinearly' (with too little or too much dopamine being detrimental to performance) related to working memory. Surprisingly, hippocampal D1 receptor binding had no association with any memory and prefrontal functions.	H. Takahashi, M. Kato, H. Takano, R. Arakawa, M. Okumura, T. Otsuka, F. Kodaka, M. Hayashi, Y. Okubo, H. Ito, T. Suhara Differential contributions of prefrontal and hippocampal dopamine D1 and D2 receptors in human cognitive functions. J. Neurosci., 28 (2008), pp. 12032–12038
Using PET and the radioligand SCH 23390, a recent study could not find any linear or curvilinear relationship between D1 receptor binding potential for dorsolateral prefrontal cortex and perseverative errors in the Wisconsin Card Sorting Test and performance in other cognitive tasks. However, D1 receptor binding potential in hippocampus was positively linked to executive performance as well as to speed and knowledge and in associative striatum it was more strongly linked to general knowledge.	Karlsson S, Rieckmann A, Karlsson P, Farde L, Nyberg L, Bäckman L. Relationship of dopamine D1 receptor binding in striatal and extrastriatal regions to cognitive functioning in healthy humans. Neuroimage. 2011 Jul 15;57(2):346-51.
Striatal D1 binding potential in 20 younger (22-30 years) and 20 older (65-75 years) persons who underwent two [^{11}C]SCH 23390 PET measurements, one while resting and one while performing a cognitive task taxing inhibitory functioning was examined. The younger persons showed significant task-related reductions of D1 binding in sensorimotor, limbic, and associative striatum during cognitive activity compared to rest. Older persons showed no reliable binding potential reductions in any striatal subregion.	Karlsson S, Nyberg L, Karlsson P, Fischer H, Thilers P, Macdonald S, Brehmer Y, Rieckmann A, Halldin C, Farde L, Bäckman L. Modulation of striatal dopamine D1 binding by cognitive processing. Neuroimage. 2009 Nov 1;48(2):398-404.
Altered prefrontal and parietal D1 receptor density was recently demonstrated during resting state after five weeks of working memory (cognitive) training as studied with [^{11}C]SCH 23390 PET in 13 volunteers (healthy males 20 to 28 years old)	F. McNab, A. Varrone, L. Farde, A. Jucaite, P. Bystritsky, H. Forssberg, T. Klingberg. Changes in cortical dopamine D1 receptor binding associated with cognitive training. Science, 323 (2009), pp. 800–802
Spatial working memory performance and associated fMRI activity were compared in between two groups of younger adults one with [^{11}C]SCH 23390 and the other under placebo conditions as well as with a group of healthy elderly adults. As expected a load-dependent working memory effect in fronto-parietal regions along with age-related reductions within the same network were observed. Moreover, younger adults under the influence of SCH 23390 hampered both cognitive performance and functional brain activity by showing reduced accuracy in the SWM task accompanied by reduced load-dependent BOLD activity in the same fronto-parietal regions, with the strongest effect seen in frontal cortex. This is further supported by the PET findings, which showed a 50% blockade of D1 receptors after SCH 23390	Fischer H, Nyberg L, Karlsson S, Karlsson P, Brehmer Y, Rieckmann A, MacDonald SW, Farde L, Bäckman L. Simulating neurocognitive aging: effects of a dopaminergic antagonist on brain activity during working memory. Biol Psychiatry. 2010 Mar 15;67(6):575-80.
Persistent, long-term memory of rapid, hippocampal-mediated	Bethus I, Tse D, Morris RG. Dopamine and memory: modulation of the persistence of

acquisition of new paired associates requires activation of D1 receptor in hippocampus at or around the time of encoding as studied with intrahippocampal infusion of SCH 23390 in experiments using an episodic-like memory task in rats	memory for novel hippocampal NMDA receptor-dependent paired associates. J Neurosci. 2010 Feb 3;30(5):1610-8.
Either an acute tail-hanging stress or a single *ip* dose of SCH 23390 significantly decreased the step-through latency in the one-trial step-through task. However, SCH 23390 prevented the acute tail-hanging stress-induced decrease in the step-through latency. In addition, the effects of tail-hanging stress and/or SCH 23390 on the changes in step-through latency were not through non-memory factors such as nociceptive perception and motor function. Data indicate that the hyperactivation of dopamine D1 receptors mediated the stress-induced deficit of emotional learning and memory.	Wang Y, Wu J, Zhu B, Li C, Cai JX. Dopamine D1 receptors are responsible for stress-induced emotional memory deficit in mice. Stress. 2012 Mar;15(2):237-42.

Schizophrenia

A number of previously published homogenate receptor binding studies have postulated that dopaminergic dysfunction in schizophrenia may be related to abnormalities in dopamine receptors. Though recent results do not always replicate previous postmortem and PET findings of altered central dopamine D1 receptor binding in schizophrenia.

D_1 receptor density ([^{3}H]SCH 233900) was reduced by 43% in postmortem caudate brains from 8 schizophrenic patients as compared with 8 normal subjects while the D_2 receptor density exhibited a 56% increase	Hess E.J., Bracha H.S., Kleinman J.E., Creese I. *Dopamine receptor subtype imbalance in schizophrenia.* Life Sci. 1987;40(15):1487–97.
[^{11}C]SCH 23390 PET was able to assess striatal dopamine receptor occupancies in patients treated with various antipsychotic drugs. Clinical antipsychotic drug treatment with sulpiride and cis(Z)-flupentixol decanoate causes a substantial blockade of D2-dopamine receptors in the basal ganglia but has only a minor effect on D1-dopamine receptors	Farde L., Hall H. *Positron emission tomography--examination of chemical transmission in the living human brain. Development of radioligands.* Arzneimittelforschung. 1992;42(2A):260–4. Farde L, Halldin C, Stone-Elander S, Sedvall G. PET analysis of human dopamine receptor subtypes using 11C-SCH 23390 and 11C-raclopride. Psychopharmacology (Berl). 1987;92(3):278-84.
[^{3}H]SCH 233900 autoradiography of postmortem striatal specimens (from patients with schizophrenia, normal controls, and psychiatric controls that had received neuroleptics) failed to define significant differences between the study groups	Knable MB, Hyde TM, Herman MM, Carter JM, Bigelow L, Kleinman JE. Quantitative autoradiography of dopamine-D1 receptors, D2 receptors, and dopamine uptake sites in postmortem striatal specimens from schizophrenic patients. Biol Psychiatry. 1994 Dec 15;36(12):827-35. PubMed PMID: 7893846.
Using [^{11}C]SCH 23390 PET, binding to D1 receptors did not differ significantly between subjects with schizophrenia (first-admission, neuroleptic-naive) and healthy subjects in any of the brain regions	Karlsson P, Farde L, Halldin C, Sedvall G. PET study of D(1) dopamine receptor binding in neuroleptic-naive patients with schizophrenia. Am J Psychiatry. 2002 May;159(5):761-7. PubMed PMID: 11986129.
There was a highly significant reduction of the D1 signal in high intensity regions of the basal ganglia when compared in young drug naive schizophrenic patients and age matched control subjects using [^{11}C]SCH 23390 PET	Sedvall G, Pauli S, Karlsson P, Farde L, Nordström AL, Nyberg S, Halldin C. PET imaging of neuroreceptors in schizophrenia. Eur Neuropsychopharmacol. 1995;5 Suppl:25-30. Review.
In patients with chronic schizophrenia in severe residual phase with chronic antipsychotic treatment, the binding potential value of [^{11}C]SCH 23390 as measured by PET was significantly lower in the striatum and cortical regions than those of healthy controls.	Kosaka J, Takahashi H, Ito H, Takano A, Fujimura Y, Matsumoto R, Nozaki S, Yasuno F, Okubo Y, Kishimoto T, Suhara T. Decreased binding of [11C]NNC112 and [11C]SCH23390 in patients with chronic schizophrenia. Life Sci. 2010 May

Abnormality of cognitive function in schizophrenia has been suggested to be related to reduced dopamine D1 receptor	22;86(21-22):814-8. Epub 2010 Mar 30.
The amplitude of the acoustic startle response is decreased if the startle stimulus is preceded by a non-startle eliciting stimulus. This sensorimotor gating phenomenon, known as prepulse inhibition, is diminished in schizophrenic individuals. In rats, the dopamine agonist apomorphine disrupts prepulse inhibition and this disruption is reversed by classical and atypical antipsychotics. Pretreatment with the D1 antagonist SCH 23390 (0.01, 0.05, 0.1 mg/kg SC) or the D2 antagonist eticlopride (0.01, 0.05, 0.1 mg/kg SC) attenuated the disruptive effects of apomorphine. These results indicate that selective blockade of either the D1 or D2 receptor subtype is sufficient in reversing the sensorimotor gating deficits produced by apomorphine.	Hoffman DC, Donovan H. D1 and D2 dopamine receptor antagonists reverse prepulse inhibition deficits in an animal model of schizophrenia. Psychopharmacology (Berl). 1994 Aug;115(4):447-53. PubMed PMID: 7871088.
Quetiapine alleviates both positive and negative symptoms as well as certain cognitive impairments in schizophrenia and may also be used as monotherapy in bipolar and major depressive disorder. The combination of low, clinically relevant concentrations of quetiapine (60nM) and reboxetine (20nM) markedly facilitated cortical NMDA receptor-mediated transmission, an effect that could be inhibited by SCH 23390. The author concluded that concomitant norepinephrine transporter -inhibition by norquetiapine, the major metabolite of quetiapine in humans, may contribute to the overall antipsychotic effectiveness of quetiapine in spite of its relatively low level of D2 occupancy	Björkholm C, Jardemark K, Marcus MM, Malmerfelt A, Nyberg S, Schilström B,Svensson TH. Role of concomitant inhibition of the norepinephrine transporter for the antipsychotic effect of quetiapine. Eur Neuropsychopharmacol. 2012 Jun 23. [Epub ahead of print] PubMed PMID: 22732518.

Obsessive-compulsive disorder (OCD) / Impulsivity / ADHD

Using PET, the binding potentials for [^{11}C]SCH 23390 at D1 receptors in seven drug-free obsessive-compulsive disorder (OCD) patients was significantly reduced in both caudate nucleus and putamen compared with healthy controls. No correlations were found between D1 binding potentials and symptom measures. The finding of D1 downregulation suggests an increased nigrostriatal dopaminergic drive in OCD which provides support for trials of novel treatments in obsessive-compulsive disorder based on dopaminergic system blockade.	Olver JS, O'Keefe G, Jones GR, Burrows GD, Tochon-Danguy HJ, Ackermann U,Scott A, Norman TR. Dopamine D1 receptor binding in the striatum of patients with obsessive-compulsive disorder. J Affect Disord. 2009 Apr;114(1-3):321-6.
There is a hyperactivation of the anterior cingulate cortex during provocation of symptoms and conflict-inhibition tasks in patients with obsessive-compulsive disorder. Using [^{11}C]SCH 23390 PET, a significant reduction of D1 binding potentials in anterior cingulate cortex was observed in seven drug-free OCD patients compared with matched healthy controls. These findings suggest mesocortical dopamine inputs via D1 receptors may play a role in the aetiology of OCD.	Olver JS, O'Keefe G, Jones GR, Burrows GD, Tochon-Danguy HJ, Ackermann U, Scott AM, Norman TR. Dopamine D(1) receptor binding in the anterior cingulated cortex of patients with obsessive-compulsive disorder. Psychiatry Res. 2010 Jul 30;183(1):85-8. Epub 2010 Jun 9. PubMed PMID: 20538439.
Recent data implicate both the orbitofrontal cortex (OFC) and the dopaminergic system in psychiatric disorders associated with high levels of impulsivity, including substance abuse, mania and obsessive-compulsive disorder. Intra-OFC administration of SCH 23390 decreased impulsive responding in highly impulsive rats, but did not affect behaviour in less impulsive animals as assessed in rats performing the five-choice serial reaction time test of attention and motor impulsivity.	Winstanley CA, Zeeb FD, Bedard A, Fu K, Lai B, Steele C, Wong AC. Dopaminergic modulation of the orbitofrontal cortex affects attention, motivation and impulsive responding in rats performing the five-choice serial reaction time task. Behav Brain Res. 2010 Jul 11;210(2):263-72.

A neuropsychological hallmark of attention deficit/hyperactivity disorder (ADHD) is the reduced ability to tolerate delay of reinforcement, leading to impulsive choice. A significant positive correlation between impulsive choice and transcript levels of the D1 dopamine receptor in the rat medial prefrontal cortex was observed. Again, local medial prefrontal cortex infusions of SCH 23390 and agonist SKF 38393 resulted in increased impulsive choice.	Loos M, Pattij T, Janssen MC, Counotte DS, Schoffelmeer AN, Smit AB, Spijker S, van Gaalen MM. Dopamine receptor D1/D5 gene expression in the medial prefrontal cortex predicts impulsive choice in rats. Cereb Cortex. 2010 May;20(5):1064-70.
Spontaneously hypertensive rats (SHR) are widely used as a rat model of ADHD. Brain mapping analysis of Fos-immunoreactivity revealed that SHR showed a marked increase in Fos expression in the core part of the nucleus accumbens. Treatment of SHR with SCH 23390 significantly reversed both behavioural hyperactivity and elevated Fos expression in the core part of the nucleus accumbens and cerebral cortex.	Ohno Y, Okano M, Masui A, Imaki J, Egawa M, Yoshihara C, Tatara A, Mizuguchi Y, Sasa M, Shimizu S. Region-specific elevation of D_1 receptor-mediated neurotransmission in the nucleus accumbens of SHR, a rat model of attention deficit/hyperactivity disorder. Neuropharmacology. 2012 Sep;63(4):547-54.
Rats were trained to self-administer methylphenidate (0.25 mg per infusion) via an intravenous catheter according to a fixed ratio 1 (FR1) or progressive ratio (PR) schedule. Treatment with SCH 23390 or eticlopride increased the number methylphenidate infusions taken by rats on the FR1 schedule and reduced breaking points on the PR schedule. These results demonstrate that intravenous methylphenidate is a reinforcer and that its reinforcing efficacy is related to increased dopamine activity at D1 and D2 receptors.	Botly LC, Burton CL, Rizos Z, Fletcher PJ. Characterization of methylphenidate self-administration and reinstatement in the rat. Psychopharmacology (Berl). 2008 Jul;199(1):55-66.
Optimal doses of methylphenidate or atomoxetine improved prefrontal cortex cognitive function in monkeys. These enhancing effects were blocked by idazoxan or SCH 23390 which support a likely contribution of these receptors to their therapeutic effects in the treatment of attention-deficit/hyperactivity disorder.	Gamo NJ, Wang M, Arnsten AF. Methylphenidate and atomoxetine enhance prefrontal function through α2-adrenergic and dopamine D1 receptors. J Am Acad Child Adolesc Psychiatry. 2010 Oct;49(10):1011-23.
Intravenous methylphenidate activates the firing activity of medial prefrontal cortex neurones in anaesthetised rats. Local diffusion or systemic administration of SCH 23390 partially reduced this activity.	Gronier B. In vivo electrophysiological effects of methylphenidate in the prefrontal cortex: involvement of dopamine D1 and alpha 2 adrenergic receptors. Eur Neuropsychopharmacol. 2011 Feb;21(2):192-204.
Previous studies demonstrated that cocaine and methamphetamine differentially alter rat brain neurotensin systems through dopaminergic mechanisms. The neurotensin-like immunoreactivity changes in basal ganglia regions induced by methylphenidate were prevented when SCH 23390 or eticlopride were co-administered with methylphenidate.	Alburges ME, Hoonakker AJ, Horner KA, Fleckenstein AE, Hanson GR. Methylphenidate alters basal ganglia neurotensin systems through dopaminergic mechanisms: a comparison with cocaine treatment. J Neurochem. 2011 May;117(3):470-8.

Drug Overdose

In rats SCH 23390 offered significant protection from death in dextroamphetamine overdosage, without providing protection from death by methamphetamine overdose. The compound provided significant protection from cocaine overdose in rats only at the lowest dose tested in the measurement series.	Derlet, R. W.; Albertson, T. E.; Rice, P. (1990). "The Effect of SCH 23390 Against Toxic Doses of Cocaine, d-Amphetamine and Methamphetamine". *Life Sciences* **47** (9): 821–827.
Both cocaine and the stable charged cocaine analogue, cocaine methiodide produced dose-related increases in lethality in male, Swiss Webster mice. Several dopamine D1 antagonists including SCH 23390 produced dose-dependent protection against the lethal effects of both compounds.	Witkin JM, Newman AH, Nowak G, Katz JL. Role of dopamine D1 receptors in the lethal effects of cocaine and a quaternary methiodide analog. J Pharmacol Exp Ther. 1993 Oct;267(1):266-74.

Addiction

Experiments using SCH 23390 suggest that the reinforcing effects of food, water, saccharin, heroin and brain stimulation all critically depend on the activation of D1 dopamine receptors, particularly those in the nucleus accumbens and the ventral tegmental area.	Nakajima S. Subtypes of dopamine receptors involved in the mechanism of reinforcement. Neurosci Biobehav Rev. 1989 Summer-Fall;13(2-3):123-8. Review.
SCH 23390 or the D2 receptor antagonist, eticlopride attenuated the potentiation of drug-seeking produced by MDMA self-administration.	Schenk S, Gittings D, Colussi-Mas J. Dopaminergic mechanisms of reinstatement of MDMA-seeking behaviour in rats. Br J Pharmacol. 2011 Apr;162(8):1770-80.
Dopamine D1 and D2 receptors in striatum, like nigral D1 receptors, are needed for methamphetamine-induced striatal dopamine transporter reductions.	Gross NB, Duncker PC, Marshall JF. Striatal dopamine D1 and D2 receptors: widespread influences on methamphetamine-induced dopamine and serotonin neurotoxicity. Synapse. 2011 Nov;65(11):1144-55.
Administration of SCH 23390 and D2 receptor antagonists (raclopride) reduced gratification of sodium appetite triggered by sodium deficiency. SCH 23390 was specific, having no effect on osmotic-induced water drinking. Bilateral microinjection of SCH 23390 (100 nM in 200 nL) into rats' lateral hypothalamus greatly reduced sodium appetite. Gene set enrichment analysis in hypothalami of mice with sodium appetite showed significant enrichment of gene sets previously linked to addiction (opiates and cocaine) .	Liedtke WB, McKinley MJ, Walker LL, Zhang H, Pfenning AR, Drago J, Hochendoner SJ, Hilton DL, Lawrence AJ, Denton DA. Relation of addiction genes to hypothalamic gene changes subserving genesis and gratification of a classic instinct, sodium appetite. Proc Natl Acad Sci U S A. 2011 Jul 26;108(30):12509-14.
The inhibitory effect of glutamate receptor antagonists on the conditioned place aversion induced by naloxone-precipitated withdrawal after a single morphine exposure could be blocked by D1 and D2 dopamine receptor antagonists, including SCH 23390, suggesting the involvement of a glutamatergic-dopaminergic interaction.	Kawasaki Y, Araki H, Suemaru K, Kitamura Y, Gomita Y, Sendo T. Involvement of dopaminergic receptor signaling in the effects of glutamatergic receptor antagonists on conditioned place aversion induced by naloxone in single-dose morphine-treated rats. J Pharmacol Sci. 2011;117(1):27-33.
Intermittent exposure to cocaine (10 μM) significantly enhanced ryanodine receptor 1 and 2 proteins and their mRNA which were dose-dependently blocked by SCH 23390, but not by a dopamine D2 receptor antagonist (sulpiride). These results indicate a regulatory role of dopamine D1 receptors in ryanodine receptor expression by cocaine. The levels of ryanodine receptors -1 and -2 in the limbic forebrain and frontal cortex significantly increased in the cocaine-conditioned mice (using the place preference procedure) which was completely abolished by SCH 23390, but not by sulpiride.	Kurokawa K, Mizuno K, Shibasaki M, Kiyokage E, Toida K, Ohkuma S. Cocaine increases ryanodine receptors via dopamine D1 receptors. Synapse. 2011 Oct;65(10):1106-12. doi: 10.1002/syn.20935. Kurokawa K, Mizuno K, Shibasaki M, Ohkuma S. Dopamine D(1) receptors participate in cocaine-induced place preference via regulation of ryanodine receptor expression. J Pharmacol Sci. 2011;117(2):87-97.
Systemic SCH 23390 reduced sucrose seeking after 1 day of forced abstinence, significantly reducing responding following pretreatment with 1, 5, and 25 μg/kg SCH 23390, but only 25 μg/kg significantly reduced sucrose seeking after 30 days of forced abstinence. SCH 23390 (0.3 or 0.6 μg/site) in the core or shell of the nucleus accumbens reduced sucrose seeking in all groups.	Grimm JW, Harkness JH, Ratliff C, Barnes J, North K, Collins S. Effects of systemic or nucleus accumbens-directed dopamine D1 receptor antagonism on sucrose seeking in rats. Psychopharmacology (Berl). 2011 Jul;216(2):219-33.
Concomitant administration of ethanol with D1 (SCH 23390, 0-0.03 mg/kg) but not D2 antagonist prevented the expression of ethanol sensitization, suggesting that the neuroadaptations underlying ethanol behavioural sensitization depend preferentially on D1 receptor actions.	Camarini R, Marcourakis T, Teodorov E, Yonamine M, Calil HM. Ethanol-induced sensitization depends preferentially on D1 rather than D2 dopamine receptors. Pharmacol Biochem Behav. 2011 Apr;98(2):173-80.
Cocaine-induced conditioned place preference in zebrafish was blocked by Sulpiride, a potent D2 receptor antagonist while SCH	Darland T, Mauch JT, Meier EM, Hagan SJ, Dowling JE, Darland DC. Sulpiride, but not SCH23390, modifies cocaine-

23390 had no effect.	induced conditioned place preference and expression of tyrosine hydroxylase and elongation factor 1α in zebrafish. Pharmacol Biochem Behav. 2012 Aug 15;103(2):157-167.
Alterations in nitric oxide release in response to psychostimulants in the striatum cause a plastic change contributing to the development and expression of addiction. Acute systemic injection of cocaine (20 mg/kg) increased NO efflux, which was reduced by the intrastriatal infusion of SCH 23390 (7.5 nmol)	Lee DK, Ahn SM, Shim YB, Koh WC, Shim I, Choe ES. Interactions of Dopamine D1 and N-methyl-D-Aspartate Receptors are Required for Acute Cocaine-Evoked Nitric Oxide Efflux in the Dorsal Striatum. Exp Neurobiol. 2011 Jun;20(2):116-22.
Microinjections of the DA D1 receptor antagonist SCH 23390 into either the rat prefrontal cortex, nucleus accumbens, or central or basolateral amygdala have been demonstrated to block the discriminative stimulus properties of cocaine.	Callahan PM, De La Garza R 2nd, Cunningham KA. Mediation of the discriminative stimulus properties of cocaine by mesocorticolimbic dopamine systems. Pharmacol Biochem Behav. 1997 Jul;57(3):601-7.Review.
The c-fos and junB immediate early genes were induced in neurons of the medial and ventral striatum following administration of morphine. The striatal induction of c-fos and junB mRNA and Fos protein was blocked by SCH 23390. Since the pattern of the morphine induction of c-fos and junB in striatum and nucleus accumbens was similar to that observed with cocaine and amphetamine, these data support current concepts that limbic striatum and nucleus accumbens are among the brain regions that mediate drug abuse.	Sharp FR, Liu J, Nickolenko J, Bontempi B. NMDA and D1 receptors mediate induction of c-fos and junB genes in striatum following morphine administration: implications for studies of memory. Behav Brain Res. 1995 Jan 23;66(1-2):225-30.Review.
Like c-fos, zif268, a transcription regulatory factor that is expressed at high levels in brain neurons, is markedly activated in striatum by cocaine and amphetamine. This response appears to involve the dopamine system, since it is abolished by SCH 23390.	Bhat RV, Cole AJ, Baraban JM. Role of monoamine systems in activation of zif268 by cocaine. J Psychiatry Neurosci. 1992 Sep;17(3):94-102. Review.
The place preference induced by phencyclidine (PCP, 8 mg/kg) in wild-type mice pretreated with PCP (10 mg/kg/day for 28 days) was attenuated by SCH 23390	Noda Y, Nabeshima T. Involvement of signal transduction cascade via dopamine-D1 receptors in phencyclidine dependence. Ann N Y Acad Sci. 2004 Oct;1025:62-8. Review.
Rats were trained to discriminate SKF 38393 (10 mg/kg) from saline in a two-lever situation involving fixed-ratio extinction schedules of water reinforcement, the effects of which were blocked by the SCH 23390 but not by haloperidol.	Appel JB, Weathersby RT, Cunningham KA, Callahan PM, Barrett RL. Stimulus properties of dopaminergic drugs: comparisons involving selective agonists and antagonists. Psychopharmacol Ser. 1988;4:44-56. Review.
Animals predisposed to run high distances on a nightly basis may quickly develop a rewarding response to exercise due to an optimal D1-like receptor signalling pathway in the nucleus accumbens that can be perturbed by either activation with SKF 82958 or blocking with SCH 23390	Roberts MD, Gilpin L, Parker KE, Childs TE, Will MJ, Booth FW. Dopamine D1 receptor modulation in nucleus accumbens lowers voluntary wheel running in rats bred to run high distances. Physiol Behav. 2012 Feb 1;105(3):661-8.
SCH 23390 and D2 receptor antagonist sulpiride administrated into the CA1 region of hippocampus (dorsal hippocampus) significantly decreased the rewarding effects of intra-VTA administration of morphine using the conditioned place preference in rats	Esmaeili MH, Kermani M, Parvishan A, Haghparast A. Role of D1/D2 dopamine receptors in the CA1 region of the rat hippocampus in the rewarding effects of morphine administered into the ventral tegmental area. Behav Brain Res. 2012