Biochemical Pharmacology, Vol. 52, pp. 511–518, 1996.

ISSN 0006-2952/96/$15.00 + 0.00
PII S0006-2952(96)00239-0

COMMENTARY

Aminotetralin Drugs and D_3 Receptor Functions

WHAT MAY PARTIALLY SELECTIVE D_3 RECEPTOR LIGANDS TELL US ABOUT DOPAMINE D_3 RECEPTOR FUNCTIONS?

*Daniel Lévesque**

DEPARTMENT OF PHARMACOLOGY, FACULTY OF MEDICINE, LAVAL UNIVERSITY, CITÉ UNIVERSITAIRE, QUÉBEC, G1K 7P4 CANADA

ABSTRACT. The dopamine D_3 receptor gene was identified by Sokoloff and colleagues in 1990. This finding rapidly gained the interest of the scientific community because this unexpected dopamine receptor subtype may play an important role in the antipsychotic activity of neuroleptic drugs. It recognizes most neuroleptics with a high affinity, and its brain distribution is restricted mainly to the ventral part of the striatal complex. However, the characterization and the subsequent identification of functions of the D_3 receptor were hampered initially by at least four important factors that are still partially unresolved: (1) the absence of selective drugs that can discriminate between the D_2 and D_3 receptor subtype functions *in vivo*, (2) the lack of apparent coupling with GTP-dependent proteins, (3) the absence of effects on second messenger systems, and (4) the low level of expression of this receptor in brain tissue; these factors have contributed to tempering the interest of scientists. However, this situation has begun to change with the identification of [^{3}H]7-hydroxy-*N*,*N*-(di-*n*-propyl)-2-aminotetralin ([^{3}H]7-OH-DPAT), the first selective ligand for the dopamine D_3 receptor. Although its binding selectivity for the D_3 versus the D_2 receptor is somewhat artificial, the potentially important impact of identification of a function for the D_3 receptor encouraged scientists to use this aminotetralin compound for *in vivo* studies with, however, limited success. This commentary is focused on the impact and controversies generated by the use of 7-OH-DPAT and its congeners, on new conceptual views that may arise from this research, and on what partially selective D_3 receptor ligands may tell us about dopamine D_3 receptor functions. BIOCHEM PHARMACOL 52;4: 511–518, 1996.

KEY WORDS. 7-OH-DPAT; aminotetralin; dopamine D_2 receptor; dopamine D_3 receptor; autoreceptor; locomotion; cocaine; rat

[^{3}H]7-OH-DPAT AS A D_3 RECEPTOR SELECTIVE LIGAND

The identification of a D_3 receptor ligand was an important challenge because its pharmacology, as observed using heterologous expression in transfected cells [1], is similar to the pharmacology of the D_2 receptor and also because D_3 receptor expression is estimated at 1–10% of the total D_2-like receptor protein expression in the forebrain [2–4]. 7-OH-DPAT† is not a new drug. It was synthesized in the early 1980s and identified as a D_2-like autoreceptor-preferring agonist [5–9]. However, we have identified a new property of the drug, i.e. its ability to selectively bind to the D_3 receptor in specific binding conditions [3]. It is important to emphasize the fact that the selectivity of 7-OH-DPAT for the D_3 receptor in radioligand binding assays is totally dependent on assay conditions. Magnesium ions should be absent and EDTA must be added in both tissue homogenate and binding assay buffers. This is the most critical point to achieve the selectivity observed [3]. Moreover, Tris buffer does not perform as well as HEPES buffer for the binding assay (unpublished observation), and keeping a moderate concentration of NaCl (not above 50 mM) is also required [3]. Under these conditions, the binding of 7-OH-DPAT to the D_2 receptor is abolished almost completely [3, 10], and it is not necessary to add a non-hydrolysable GTP analog to convert the high affinity state into the low affinity state of the D_2 receptor. Extensive washes of tissue homogenate preparations, as well as of tissue sections in autoradiography studies, are also essential to dissociate the endogenous dopamine from the D_3 receptor binding site [3, 11]. Neglect of these prerequisites may lead to false interpretations. For example, a receptor capacity as high as 125 fmol/mg of protein has been reported for D_3 receptors, and 4 months of exposure in receptor autoradiography were re-

* Correspondence: Dr. Daniel Lévesque, Molecular Endocrinology Laboratory, CHUL Research Centre, 2705 Blvd. Laurier, Québec (Québec), G1V 4G2 Canada. Tel (418)654-2296; FAX (418)654-2761; E-mail: Daniel.Levesque@crchul.ulaval.ca

† *Abbreviations:* 7-OH-DPAT, 7-hydroxy-*N*,*N*-(di-*n*-propyl)-2-aminotetralin; NEM, *N*-ethylmaleimide; [^{125}I]*R*(+)-7-OH-PIPAT, [^{125}I]*R*(+)-7-hydroxy-2-(*N*-*n*-propyl-*N*-3′-iodo-2′-propenyl)aminotetralin; [^{125}I]*R*(+)-5-OH-PIPAT, [^{125}I]*R*(+)-5-hydroxy-2-(*N*-*n*-propyl-*N*-3′-iodo-2′-propenyl)aminotetralin; EEDQ, *N*-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline; 6-OHDA, 6-hydroxydopamine; [^{3}H]*S*(+)-PD-128,907, [^{3}H]4a*R*,10b*R*-(+)-*trans*-3,4,4a,10b-tetrahydro-4-propyl-2*H*,5*H*-[1]benzopyrano[4,3-*b*]-1,4-oxazin-9-o1; (+)-S-14297, (+)-[7(*N*,*N*-dipropylamino)-5,6,7,8-tetrahydro-naphtho(2,3-*b*)dihydro-2,3-furane]; Nafadotride, *N*-[(n-butyl-2-pyrrolidinyl)methyl]-1-methoxy-4-cyano-naphtalene-2-carboxamide; (−)DS121, *S*-(−)-3-(3-cyanophenyl)-*N*-*n*-propyl piperidine; U99194A, 5,6-di-methoxy-2-(dipropylamino) indan hydrochloride; and Gpp(NH)p, guanosine 5′[β-γ-imido]triphosphate.

quired because of the presence of $MgCl_2$ in tissue homogenate preparations and, possibly, insufficient washing procedures, respectively [12, 13]. The D_3 receptor binding site has also been claimed to be modulated by pretreatment with the alkylating agent NEM [13]. However, the binding capacity of D_3 receptors obtained in the presence of NEM (about 25 fmol/mg of protein) is somewhat similar to the D_3 receptor levels in the absence of NEM reported by others [3, 14–16]. The inappropriate binding assay for selectively labeled D_3 receptor with [^{3}H]7-OH-DPAT and binding capacities obtained with and without NEM suggest that the effect observed in this study mostly reflects the actions of NEM on the D_2 high affinity state that is labeled by [^{3}H]7-OH-DPAT under these conditions [13]. D_3 receptors are, in fact, resistant to the effect of *in vivo* NEM treatment. This interpretation is consistent with the result showing that D_3 receptors are affected modestly by administration of *in vivo* EEDQ, another non-selective alkylating agent that produces irreversible inactivation of aminergic receptors [17].

The affinity of [^{3}H]7-OH-DPAT for the sigma$_1$ binding site [16, 18] can be easily overcome by maintaining a low concentration of radioligand. In autoradiographic studies, for example, a concentration that is not over 1.0 to 2.0 nM is recommended. The use of a pure selective dopamine agent for evaluation of non-specific binding is also required because the sigma binding site appears "beyond the maximal inhibition of [^{3}H]7-OH-DPAT binding produced by dopamine" [18]. For saturation or competition studies where higher than 10 nM concentrations of labeled or unlabeled 7-OH-DPAT are used, the addition of a sigma blocker is recommended [16]. Interestingly enough, most D_3 receptor ligands investigated show good affinities for the sigma binding site. On the contrary, the formerly identified sigma selective drug *R*(−)-PPAP [*R*(−)-*N*-(3-phenyl-1-propyl)-1-phenyl-2-aminopropane], previously shown to be devoid of dopaminergic activity, displaces binding to D_3 receptors [16]. In addition, the sigma binding site labeled with [^{3}H]pentazocine in human cerebellum homogenates is not affected by $MgCl_2$ or GTP analogs [19], two characteristics shared with the D_3 receptor binding site. In the human brain, the D_3 receptor binding site is not restricted to cerebellar lobules 9 and 10, as in the rat cerebellum [20]. Hence, is [^{3}H]pentazocine binding really selective for the sigma binding site? More extensive and systematic analyses of sigma ligand affinities for D_3 receptors are needed in order to understand the relationship between these two binding sites. On the other hand, addition of a GTP analog or the absence of $MgCl_2$ in binding assays for D_3 receptor, as well as the restricted expression of this receptor in brain structures that cannot be easily dissected out, is probably responsible for an underestimation of D_3 receptor binding sites.

The magnitude of the GTP effect on the agonist affinity states of the D_3 receptor in transfected cells is generally small or absent [1, 21–25]. Moreover, no consistent coupling of the receptor with known second messenger pathways has been observed in a variety of heterologous expression systems [1, 23, 24, 26–28]. When a coupling with second messenger pathways was observed, such as inhibition of forskolin-stimulated cyclic AMP or calcium current, the intensity of the effect was small [22, 29, 30]. However, a recent study showed a very strong effect of the D_3 receptor stimulation on cyclic AMP levels in a transfected neuroblastoma/glioma hybrid (NG108-15) cell clone [31]. The appropriate G protein that coupled to the D_3 receptor may not be expressed in all the cell lines studied, but pertussis toxin-sensitive intracellular responses can be observed in some cell lines [22, 28, 32], and stimulation of the D_3 receptor in transfected HEK-293 cells increases [^{35}S]GTPγS binding [33]. Moreover, in brain tissue, in conditions that favor the high affinity state of D_2-like receptor subtypes as well as the effect of GTP, i.e. in the presence of $MgCl_2$ and NaCl, and using [^{125}I]iodosulpride binding in rat cerebellum (a D_3 prototypic brain area), a complete conversion of the high into the low affinity state of the receptor was observed (Fig. 1) [3]. A similar complete conversion of the high affinity state has also been observed in the NG108-15 cell line transfected with the D_3 receptor [28]. The effect, however, is somewhat masked by closer values of the high and the low affinity states, as compared to the D_2 receptor (see Fig. 1). Thus, a shift of GTP analogs, in the appropriate environment, has been observed, and it is total. This suggests that the D_3 receptor can couple

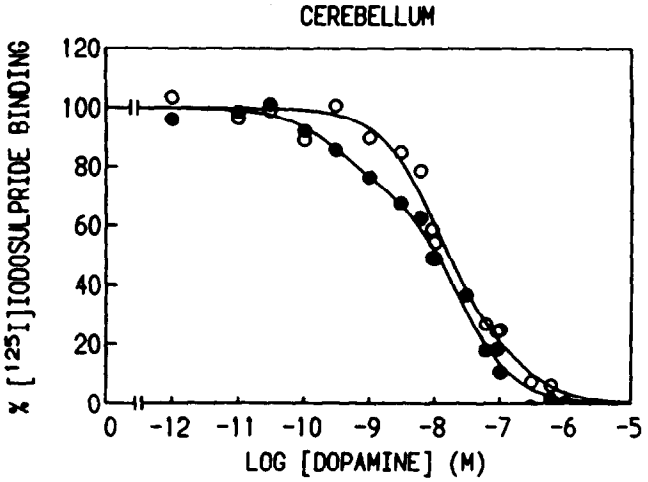

FIG. 1. Effect of Gpp(NH)p (100 μM) on inhibition of [^{125}I]iodosulpride binding by dopamine in archicerebellum (lobules 9 and 10 of the cerebellum) tissue homogenates, a D_3 prototypic structure [3]. [^{125}I]Iodosulpride was used at 0.35 nM in a buffer containing 50 mM Tris-HCl (pH 7.5), 5 mM KCl, 2 mM $MgCl_2$, 2 mM $CaCl_2$, 50 μM 8-hydroxyquinoline, 0.005% ascorbic acid, 0.1% bovine serum albumin, and 120 mM NaCl. Nonspecific binding was estimated by using 5 μM (−)-sulpiride. Key: (○) with Gpp(NH)p; and (●) without Gpp(NH)p. The curve obtained without Gpp(NH)p was best fit by a two-component biophasic curve with K_i values of 0.33± 0.15 nM (30% of sites) and 20.2 ± 0.1 nM, and this biphasic curve was totally converted to a monophasic curve in the presence of Gpp(NH)p with a K_i of 10.5 ± 1.5 nM. These results partially come from Ref. 3.

with G proteins, but the nature as well as the mode of interaction between both proteins may be distinct from that of the D_2 receptor subtype. The intensity of conformational changes of a receptor, as observed by the GTP-induced high into low agonist affinity state shift, may not be directly proportional to the intensity of the signal that is transmitted into the cell. Indeed, the effect on mitogenesis in the D_3 receptor transfected NG108–15 cells is stronger than in the D_2 transfected cells [34]. The high affinity of the D_3 receptor for dopamine, the small effect of GTP analogs, and its low level of expression in restricted brain areas may indicate that this receptor is constitutively desensitized in resting conditions. Hence, it will be only in certain situations or environments that its function can be observed. Recent theoretical considerations, based on properties of mutated adrenergic receptors that are constitutively activated, suggest the possibility of additional permitted conformations for the receptor–G protein complex. This has led to the proposition of an extended version of the ternary complex model, named the allosteric ternary complex model [35]. According to this model, receptors that displayed greater constitutive activities would have an increased affinity for endogenous agonists associated with a reduced fold apparent stimulation due to a high basal activity. Those characteristics resemble D_3 receptor properties. These mutated receptors are also constitutively phosphorylated and desensitized [36, 37]. Such a constitutive activity has been proposed recently for the naturally occurring D_{1B} receptor [38].

OTHER D_3 RECEPTOR LIGANDS

[^{3}H]7-OH-DPAT binding gave us the first direct measurement of the dopamine D_3 receptor binding site [3]. This has been confirmed by many studies using a variety of ligands. For example, [^{3}H]quinpirole binding in the presence of Gpp(NH)p [2, 39–42], and [^{3}H]quinelorane [15], [^{3}H]pramipexole [43] as well as the iodinated derivative of 7-OH-DPAT, [^{125}I]*R*(+)-7-OH-PIPAT, bindings gave similar results [44–46]. This confirms the restricted brain distribution of the D_3 receptor, previously observed at the level of its mRNA, and confirmed that the pharmacological profile observed in transfected cells is similar to that of brain tissues [1, 3, 47]. The newly synthesized iodinated aminotetralin derivatives [^{125}I]*R*(+)-7-OH-PIPAT and [^{125}I]*R*(+)-5-OH-PIPAT may represent interesting alternatives for labeling the D_3 receptor binding site, but despite their higher specific activity, their advantage over [^{3}H]*R*(+)-7-OH-DPAT is limited because they also bind the high affinity state of the D_2 receptor as well as 5-hydroxytryptamine1A, and sigma receptor subtypes [44–46, 48–50]. The recently developed ligand [^{3}H]S(+)-PD-128,907 possesses the highest binding and functional selectivity for D_3 receptors in *in vitro* models [34], but binding studies using brain tissue homogenates or sections have never been reported [51]. Thus, to date the labeled stereoselective isomer *R*(+) of 7-OH-DPAT is still the best characterized and available ligand for the D_3 receptor [52, 53]. Despite its limitations and when it is used in appropriate conditions, this ligand is a very useful tool to follow the expression of the D_3 receptor binding site in forebrain (for example, see Ref. 54). We are awaiting the next generation of ligands, including selective antagonists, that are under characterization by a number of research teams in order to fully understand the function of the D_3 receptor binding site in brain.

AMINOTETRALINS AND D_3 RECEPTOR FUNCTIONS

The *in vivo* selectivity of *R*(+)-7-OH-DPAT may be dramatically different because, as mentioned before, its selectivity for the D_3 receptor is optimized by manipulating binding assay conditions [3]. Indeed, the selectivity of *R*(+)-7-OH-DPAT in *in vitro* functional models based on the capacity to increase mitogenesis (as measured by [^{3}H]thymidine incorporation) or medium acidification by D_3 receptor stimulation in transfected cells is much less apparent. These studies indicated that *R*(+)-7-OH-DPAT is poorly selective (at most 7-fold) for the D_3 receptor in those *in vitro* functional models [22, 34, 55]. The range of selectivity obtained is somewhat similar to the binding selectivity when comparing the high affinity state of the D_2 receptor with D_3 receptor affinities [10, 56]. Indeed, most studies using 7-OH-DPAT failed to clearly ascribe functions to the D_3 receptor [57–64]. There is, however, an important caveat that has been omitted. As shown in Fig. 1, a significant fraction of D_3 receptors (30% of the total population) exists in a very high affinity state for dopamine in brain tissue [3]. To which extent this very high affinity state represents a functional state of the D_3 receptor remains to be determined. Also, agonists previously identified as partially selective *in vitro* may retain some selectivity *in vivo*. There are, in fact, other factors that may explain the lack of selectivity of (+)-7-OH-DPAT *in vivo*. Experimental designs and intrinsic properties of this drug indicate that the situation is probably more complex than previously thought.

Recent data on the regulation of the D_3 receptor expression give us some clues that may explain the lack of selectivity of 7-OH-DPAT in *in vivo* studies. In paradigms using reserpinized animals as well as after deafferentation using mechanical or chemical 6-OHDA unilateral lesions, the dopamine D_2 receptor becomes up-regulated, whereas D_3 receptor expression is not affected or is decreased, respectively [54]. In these conditions, a partially selective drug has little chance to reveal D_3 receptor activity, as was reported [60, 64–66]. On the other hand, other conditions may have favored D_3 receptor selectivity. This may be the case following *in vivo* irreversible receptor inactivation with administration of the alkylating agent EEDQ. Indeed, since D_3 receptors are probably more occupied by dopamine *in vivo* than D_2 receptors, and this can be evidenced if the tissue is not washed sufficiently before radioreceptor assay

[11], or if trying to label D_3 receptor *ex vivo* [67], the effect of inactivation by EEDQ may be less important at D_3 than D_2 receptors. In fact, EEDQ is almost inactive on the D_3 receptor *in vivo*, whereas it showed similar effects on both receptors *in vitro* [17]. Thus, after EEDQ the population of remaining dopamine receptors is probably enriched in D_3 receptors, and the functional consequence of its activation could be observed [68]. On the other hand, we cannot rule out the possibility of a mixture of effects at remaining dopamine D_2-like receptor populations.

It is interesting to note that the large receptor reserve seen at D_2 autoreceptor functions (modulation of synthesis and release of dopamine) has been seen in the presence of EEDQ [69, 70], as well as regional differences of receptor reserve between substantia nigra and the ventral tegmental area [71]. Thus, this receptor reserve may not be as important as expected, because the effect observed on autoreceptor functions in the presence of EEDQ could be attributed to D_3 receptors [68]. This helps us to understand the growing body of evidence demonstrating that the dopamine D_3 receptor may affect dopamine metabolism [72]. It is not clear, however, if these autoreceptor functions are initiated at somatodendritic [73, 74] or nerve axon [68, 75] terminals or even at postsynaptic locations via negative-feedback loops [76]. Considering the extremely low level of D_3 receptor expression in dopamine neuron cell body areas [77], the effects of D_3-preferring drugs on autoreceptor functions are quite astonishing. On the other hand, D_3 autoreceptor functions may remain silent in resting conditions, as recently proposed by Gobert and collcagues [78].

It has been proposed recently that *R*(+)-7-OH-DPAT may act as a partial agonist at D_3 receptors [22, 34, 79]. The intrinsic activity of the drug may be low in the presence of the endogenous ligand and contributes to a decrease in the apparent selectivity for the D_3 receptor *in vivo*. (+)-UH232, which has been identified previously as a D_3 receptor-preferring antagonist [1], also possesses partial agonist properties [31]. In fact, most aminotetralins that showed selectivity for the D_3 receptor have a chemical structure somewhat similar to dopamine itself [80]. Therefore, it would not be surprising to find similar results, i.e. partial agonist properties to the D_3 receptor, with other aminotetralin derivatives previously identified as dopamine agonists or antagonists. Finally, aminotetralins are very potent drugs, but their *in vivo* half-life is short due to rapid liver glucuronidation in the rat [81]. 7-OH-DPAT has been shown to be the most sensitive molecule to glucuronidation enzyme of the aminotetralin series that show dopaminergic activity, 5-OH-DPAT being less susceptible to glucuronidation and 8-OH-DPAT not glucuronidated at all [81]. Thus, the concentration of the drug that may reach the brain should be very low. Estimation of the interstitial free concentration of 7-OH-DPAT in the striatum, after intraperitoneal administration, is consistent with this assumption [82]. Again, this may have contributed to decreased functional responses from D_3 receptor stimulation by the drug, but also may have favored D_3 receptor selectivity of these drugs in the brain.

AMINOTETRALINS AND LOCOMOTION

In normal non-habituated rats, *R*(+)-7-OH-DPAT and a series of D_3 preferring agonists produce biphasic effects on spontaneous locomotor activity, i.e. suppression at low doses, followed by a gradual increase in motor activity at higher dosages [55, 83–85]. A similar but opposite biphasic effect is observed with D_3 receptor-preferring antagonists, like (+)-UH232 and (+)-AJ76. This property, however, has been attributed to preferential autoreceptor selectivity of these drugs [86]. But, results obtained with recently developed partially selective D_3 receptor antagonists are in agreement with the hypothesis that the locomotor inhibitory component of these drugs is mediated through a postsynaptic D_3 receptor (i.e. independently of autoreceptor functions) (U99194A, Nafadotride), and that blockade of D_3 receptors may not be associated with catalepsy ((+)-S-14297, Nafadotride) [83, 84, 87–93].

AMINOTETRALINS AND DRUGS OF ABUSE

Aminotetralins exert extremely potent activities on behaviors associated with drugs of abuse and reward [94–101]. 7-OH-DPAT decreases cocaine self-administration at doses that were not by themselves reinforcing [94], but also lowers the minimum effective dose of cocaine, suggesting that 7-OH-DPAT may enhance the reinforcing properties of cocaine [96]. Dopamine D_3 receptor-preferring antagonists such as (+)-AJ76, (+)-UH232, and the recently developed (−)-DS121 also decrease the rate of cocaine intake [98, 100]. But, unlike other dopamine antagonists, they also delay the onset of responding to cocaine, similar to the effect of a dopamine agonist [100]. Beside the fact that the involvement of the dopamine D_3 receptor remains to be established as well as the exact location at pre- or postsynaptic receptors of these drug effects [101], the partial agonist property of 7-OH-DPAT [34], as well as (+)-UH232 [31], may explain these apparent discrepancies.

CONCLUSION

Despite the possibility that partially selective agonists may retain their selectivity for the D_3 receptor in certain conditions *in vivo* (in the presence of EEDQ, for example), we need confirmation of the involvement of the D_3 receptor in autoreceptor functions, locomotor inhibition, as well as in cocaine intake using more selective drugs or using alternative strategies. Nevertheless, aminotetralin drugs are extremely interesting agents. Indeed, such partial agonist properties shown by D_3 receptor-preferring aminotetralins may have a therapeutic advantage over pure agonists or antagonists in the treatment of cocaine addiction, for example, because they can regulate the elevated dopaminergic

tone observed during cocaine administration (antagonist property) as well as the dopamine hypoactivity observed during withdrawal or craving (agonist property) [102]. These characteristics may also be useful in the treatment of neuropsychiatric diseases where hyper- and hypodopaminergic activities can be observed. The rapid glucuronidation of these drugs limits, however, the use of the aminotetralins, although human glucuronidation of these drugs seems less efficient than that in rats [81]. On the other hand, pure agonists and antagonists with high D_3 receptor selectivity must be developed in order to clearly understand the physiological role of this enigmatic dopamine receptor and to test the therapeutic impact of the selective blockade or stimulation of the dopamine D_3 receptor subtype.

I would like to thank Drs. Pierre Sokoloff, Pierre Falardeau, and Claude Rouillard for helpful discussions. D. L. is a scholar from the "Fonds de la Recherche en Santé du Québec (FRSQ)."

References

1. Sokoloff P, Giros B, Martres M-P, Bouthenet M-L and Schwartz J-C, Molecular cloning and characterization of a novel dopamine receptor (D_3) as a target for neuroleptics. *Nature* **347:** 146–151, 1990.
2. Gehlert DR, Gackenheimer SL, Seeman P and Schaus J, Autoradiographic localization of [^{3}H]quinpirole binding to dopamine D_2 and D_3 receptors in rat brain. *Eur J Pharmacol* **211:** 189–194, 1992.
3. Lévesque D, Diaz J, Pilon C, Martres M-P, Giros B, Souil E, Schott D, Morgat J-L, Schwartz J-C and Sokoloff P, Identification, characterization, and localization of the dopamine D_3 receptor in rat brain using 7-[^{3}H]hydroxy-*N*,*N*-di-*n*-propyl-2-aminotetralin. *Proc Natl Acad Sci USA* **89:** 8155–8159, 1992.
4. Boundy VA, Luedtke RR, Gallitano AL, Smith JE, Filtz TM, Kallen RG and Molinoff PB, Expression and characterization of the rat D_3 dopamine receptor: Pharmacologic properties and development of antibodies. *J Pharmacol Exp Ther* **264:** 1002–1011, 1993.
5. Feenstra MGP, Sumners C, Goedemoed JH, De Vries JB, Rollema H and Horn AS, A comparison of the potencies of various dopamine receptor agonists in models for pre- and postsynaptic receptor activity. *Naunyn Schmiedebergs Arch Pharmacol* **324:** 108–115, 1983.
6. Seiler MP and Markstein R, Further characterization of structural requirements for agonists at the striatal dopamine D_2 receptor and a comparison with those at the striatal dopamine D_1 receptor. Studies with a series of monohydroxyaminotetralins on acetylcholine release from rat striatum. *Mol Pharmacol* **26:** 452–457, 1984.
7. Wikström H, Andersson B, Sanchez D, Lindberg P, Arvidsson L-E, Johansson AM, Nilsson JLG, Svensson K, Hjorth S and Carlsson A, Resolved monophenolic 2-aminotetralins and 1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinolines: Structural and stereochemical considerations for centrally acting pre- and postsynaptic dopamine receptor agonists. *J Med Chem* **28:** 215–225, 1985.
8. El Mestikawi S, Glowinski J and Hamon M, Presynaptic dopamine autoreceptors control tyrosine hydroxylase activation in depolarized striatal dopaminergic terminals. *J Neurochem* **46:** 12–22, 1986.
9. Mulder TBA, De Vries JB, Dijkstra D, Wiechers JW, Grol CJ and Horn AS, Further *in vivo* and *in vitro* studies with the putative presynaptic dopamine agonist *N*,*N*-dipropyl-7-hydroxy-2-aminotetralin. *Naunyn Schmiedebergs Arch Pharmacol* **336:** 494–501, 1987.
10. Gonzalez AM and Sibley DR, [^{3}H]7-OH-DPAT is capable of labeling dopamine D_2 as well as D_3 receptors. *Eur J Pharmacol* **272:** R1–R3, 1995.
11. Schotte A, Janssen PF, Gommeren W, Luyten WH and Leysen JE, Autoradiographic evidence for the occlusion of rat brain dopamine D_3 receptors *in vivo*. *Eur J Pharmacol* **218:** 373–375, 1992.
12. Hillefors-Berglund M and von Euler G, Pharmacology of dopamine D_3 receptors in the islands of Calleja of the rat using quantitative receptor autoradiography. *Eur J Pharmacol* **261:** 179–183, 1994.
13. Liu Y, Hillefors-Berglund M and von Euler G, Modulation of dopamine D_3 receptor binding by *N*-ethylmaleimide and neurotensin. *Brain Res* **643:** 343–348, 1994.
14. Booze RM and Wallace DR, Dopamine D_2 and D_3 receptors in the rat striatum and nucleus accumbens: Use of 7-OH-DPAT and [^{125}I]-iodosulpride. *Synapse* **19:** 1–13, 1995.
15. Gackenheimer SL, Schaus JM and Gehlert DR, [^{3}H]-Quinelorane binds to D_2 and D_3 dopamine receptors in the rat brain. *J Pharmacol Exp Ther* **274:** 1558–1565, 1995.
16. Wallace DR and Booze RM, Identification of D_3 and σ receptors in the rat striatum and nucleus accumbens using (±)-7-hydroxy-*N*,*N*-di-*n*-[^{3}H]propyl-2-aminotetralin and carbetapentane. *J Neurochem* **64:** 700–710, 1995.
17. McGonigle P, McElligott S, Kung M and Kung H, *In vivo* occupancy of D_2 and D_3 receptors determined with EEDQ. *Soc Neurosci Abstr* **20**(Part 1): 526, 1994.
18. Schoemaker H, [^{3}H]7-OH-DPAT labels both dopamine D_3 receptors and σ sites in the bovine caudate nucleus. *Eur J Pharmacol* **242:** R1–R2, 1993.
19. Zabetian CP, Staley JK, Flynn DD and Mash DC, [^{3}H]-(+)-Pentazocine binding to sigma recognition sites in human cerebellum. *Life Sci* **55:** PL389–PL395, 1994.
20. Herroelen L, De Backer JP, Wilczak N, Flamez A, Vauquelin G and De Keyser J, Autoradiographic distribution of D_3-type dopamine receptors in human brain using [^{3}H]7-hydroxy-*N*,*N*-di-*n*-propyl-2-aminotetralin. *Brain Res* **648:** 222–228, 1994.
21. Castro SW and Strange PG, Coupling of D_2 and D_3 dopamine receptors to G-proteins. *FEBS Lett* **315:** 223–226, 1993.
22. Chio CL, Lajiness ME and Huff RM, Activation of heterologously expressed D_3 dopamine receptors: Comparison with D_2 dopamine receptors. *Mol Pharmacol* **45:** 51–60, 1994.
23. Freedman SB, Patel S, Marwood R, Emms F, Seabrook GR, Knowles MR and McAllister G, Expression and pharmacological characterization of the human D_3 dopamine receptor. *J Pharmacol Exp Ther* **268:** 417–426, 1994.
24. MacKenzie RG, VanLeeuwen D, Pugsley TA, Shih YH, Demattos S, Tang L, Todd RD and O'Malley KL, Characterization of the human dopamine D_3 receptor expressed in transfected cell lines. *Eur J Pharmacol* **266:** 79–85, 1994.
25. Tang L, Todd RD, Heller A and O'Malley KL, Pharmacological and functional characterization of D_2, D_3 and D_4 dopamine receptors in fibroblast and dopaminergic cell lines. *J Pharmacol Exp Ther* **268:** 495–502, 1994.
26. Sokoloff P, Andrieux M, Besançon R, Pilon C, Martres M-P, Giros B and Schwartz J-C, Pharmacology of human dopamine D_3 receptor expressed in a mammalian cell line: Comparison with D_2 receptor. *Eur J Pharmacol* **225:** 331–337, 1992.
27. Seabrook GR, Patel S, Marwood R, Emms F, Knowles MR, Freedman SB and McAllister G, Stable expression of human

D_3 dopamine receptors in GH4C1 pituitary cells. *FEBS Lett* **312:** 123–126, 1992.
28. Pilon C, Lévesque D, Dimitriadou V, Griffon N, Martres M-P, Schwartz J-C and Sokoloff P, Functional coupling of the human dopamine D_3 receptor in a transfected NG108–15 neuroblastoma-glioma hybrid cell line. *Eur J Pharmacol* **268:** 129–139, 1994.
29. Potenza MN, Graminski GF, Schmauss C and Lerner MR, Functional expression and characterization of human D_2 and D_3 dopamine receptors. *J Neurosci* **14:** 1463–1476, 1994.
30. Seabrook GR, Kemp JA, Freedman SB, Patel S, Sinclair HA and McAllister G, Functional expression of human D_3 dopamine receptors in differentiated neuroblastoma x glioma NG108–15 cells. *Br J Pharmacol* **111:** 391–393, 1994.
31. Griffon N, Pilon C, Schwartz J-C and Sokoloff P, The preferential dopamine D_3 receptor ligand, (+)-UH232, is a partial agonist. *Eur J Pharmacol* **282:** R3–R4, 1995.
32. McAllister G, Knowles MR, Ward-Booth SM, Sinclair HA, Patel S, Marwood R, Emms F, Patel S, Smith A, Seabrook GR and Freedman SB, Functional coupling of human D_2, D_3, and D_4 dopamine receptors in HEK293 cells. *J Recept Signal Transduct Res* **15:** 267–281, 1995.
33. Freedman SB, Chapman KL and Patel S, Functional coupling of human dopamine D_3 receptors stably transfected in HEK-293 cells. *Soc Neurosci Abstr* **21** (Part 1): 624, 1995.
34. Sautel F, Griffon N, Lévesque D, Pilon C, Schwartz J-C and Sokoloff P, A functional test identifies dopamine agonists selective for D_3 versus D_2 receptors. *Neuroreport* **6:** 329–332, 1995.
35. Lefkowitz RJ, Cotecchia S, Samama P and Costa T, Constitutive activity of receptors coupled to guanine nucleotide regulatory proteins. *Trends Pharmacol Sci* **14:** 303–307, 1993.
36. Ren Q, Kurose H, Lefkowitz RJ and Cotecchia S, Constitutively active mutants of the α_2-adrenergic receptor (published erratum appears in *J Biol Chem* **269:** 1566, 1994). *J Biol Chem* **268:** 16483–16487, 1993.
37. Pei G, Samama P, Lohse M, Wang M, Codina J and Lefkowitz RJ, A constitutively active mutant β_2-adrenergic receptor is constitutively desensitized and phosphorylated. *Proc Natl Acad Sci USA* **91:** 2699–2702, 1994.
38. Tiberi M and Caron MG, High agonist-independent activity is a distinguishing feature of the dopamine D_{1B} receptor subtype. *J Biol Chem* **269:** 27925–27931, 1994.
39. Levant B, Grigoriadis DE and DeSouza EB, Characterization of [^{3}H]quinpirole binding to D_2-like dopamine receptors in rat brain. *J Pharmacol Exp Ther* **262:** 929–935, 1992.
40. Gehlert DR, Quantitative autoradiography of Gpp(NH)p sensitive and insensitive [^{3}H]quinpirole binding sites in the rat brain. *Synapse* **14:** 113–120, 1993.
41. Levant B, Grigoriadis DE and DeSouza EB, [^{3}H]Quinpirole binding to putative D_2 and D_3 dopamine receptors in rat brain and pituitary gland: A quantitative autoradiographic study. *J Pharmacol Exp Ther* **264:** 991–1001, 1993.
42. Malmberg A and Mohell N, Characterization of [^{3}H]quinpirole binding to human dopamine D_{2A} and D_3 receptors: Effects of ions and guanine nucleotides. *J Pharmacol Exp Ther* **274:** 790–797, 1995.
43. Mierau J, Schneider FJ, Ensinger HA, Chio CL, Lajiness ME and Huff RM, Pramipexole binding and activation of cloned and expressed dopamine D_2, D_3, and D_4 receptors. *Eur J Pharmacol* **290:** 29–36, 1995.
44. Kung MP, Kung HF, Chumpradit S and Foulon C, *In vitro* binding of a novel dopamine D_3 receptor ligand: [^{125}I]*trans*-7-OH-PIPAT-A. *Eur J Pharmacol* **235:** 165–166, 1993.
45. Burris KD, Filtz TM, Chumpradit S, Kung M-P, Foulon C, Hensler JG, Kung HF and Molinoff PB, Characterization of [^{125}I](*R*)-*trans*-7-hydroxy-2-[*N*-propyl-*N*-(3′-iodo-2′-propenyl)amino]tetralin binding to dopamine D3 receptors in rat olfactory tubercle. *J Pharmacol Exp Ther* **268:** 935–942, 1994.
46. Kung MP, Chumpradit S, Frederick D, Garner S, Burris KD, Molinoff PB and Kung HF, Characterization of binding sites for [^{125}I]*R*(+)*trans*-7-OH-PIPAT in rat brain. *Naunyn Schmiedebergs Arch Pharmacol* **350:** 611–617, 1994.
47. Bouthenet M-L, Souil E, Martres M-P, Sokoloff P, Giros B and Schwartz J-C, Localization of dopamine D_3 receptor mRNA in the rat brain using *in situ* hybridization histochemistry: Comparison with dopamine D_2 receptor mRNA. *Brain Res* **564:** 203–219, 1991.
48. Foulon C, Kung MP and Kung HF, Synthesis of (*R,S*)-2′-*trans*-7-hydroxy-2-[*N*-*n*-propyl-*N*-(3′-iodo-2′-propenyl)-amino[tetralin (*trans*-7-OH-PIPAT): A new D_3 dopamine receptor ligand. *J Med Chem* **36:** 1499–1500, 1993.
49. Chumpradit S, Kung M-P, Vessotskie J, Foulon C, Mu M and Kung HF, Iodinated 2-aminotetralins and 3-amino-1-benzopyrans: Ligands for dopamine D2 and D3 receptors. *J Med Chem* **37:** 4245–4250, 1994.
50. Chumpradit S, Kung MP, Vessotskie J and Kung HF, Synthesis, resolution and radioiodination of *S*(−)*trans*-5-hydroxy-2-[*N,N*-propyl-*N*-(3′-iodo-2′-propenyl)amino]tetralin-*S*(−)*trans*-5-OH-PIPAT, a new dopamine D_2-like receptor ligand. *J Labelled Compd Radiopharm* **36:** 1051–1062, 1995.
51. Akunne HC, Towers P, Ellis GJ, Dijkstra D, Wikstrom H, Heffner TG, Wise LD and Pugsley TA, Characterization of binding of [^{3}H]PD-128907, a selective dopamine D_3 receptor agonist ligand, to CHO-K1 cells. *Life Sci* **57:** 1401–1410, 1995.
52. Baldessarini RJ, Kula NS, McGrath CR, Bakthavachalam V, Kebabian JW and Neumeyer JL, Isomeric selectivity at dopamine D_3 receptors. *Eur J Pharmacol* **239:** 269–270, 1993.
53. Damsma G, Bottema T, Westerink BH, Tepper PG, Dijkstra D, Pugsley TA, MacKenzie RG, Heffner TG and Wikstrom H, Pharmacological aspects of *R*-(+)-7-OH-DPAT, a putative dopamine D_3 receptor ligand. *Eur J Pharmacol* **249:** R9–R10, 1993.
54. Lévesque D, Martres M-P, Diaz J, Griffon N, Lammers CH, Sokoloff P and Schwartz J-C, A paradoxical regulation of the dopamine D_3 receptor expression suggests the involvement of an anterograde factor from dopamine neurons. *Proc Natl Acad Sci USA* **92:** 1719–1723, 1995.
55. Svensson K, Carlsson A, Hugg RM, Kling-Petersen T and Waters N, Behavioral and neurochemical data suggest functional differences between dopamine D_2 and D_3 receptors. *Eur J Pharmacol* **263:** 235–243, 1994.
56. Burris KD, Pacheco MA, Filtz TM, Kung MP, Kung HF and Molinoff PB, Lack of discrimination by agonists for D_2 and D_3 dopamine receptors. *Neuropsychopharmacology* **12:** 335–345, 1995.
57. Daly SA and Waddington JL, Behavioural effects of the putative D_3 dopamine receptor agonist 7-OH-DPAT in relation to other "D_2-like" agonists. *Neuropharmacology* **32:** 509–510, 1993.
58. McElroy J, Zeller K, Amy K, Ward K, Cawley J, Mazzola A, Keim W and Rohrbach K, *In vivo* agonist properties of 7-hydroxy-*N,N*-di-*N*-propyl-2-aminotetralin, a dopamine D_3-selective receptor ligand. *Drug Dev Res* **30:** 257–259, 1993.
59. Van den Buuse M, Effects of 7-hydroxy-*N,N*-di-*n*-propyl-aminotetralin on behaviour and blood pressure of spontaneously hypertensive rats. *Eur J Pharmacol* **243:** 169–177, 1993.
60. Ahlenius S and Salmi P, Behavioral and biochemical effects of the dopamine D_3 receptor-selective ligand, 7-OH-DPAT, in the normal and reserpine-treated rat. *Eur J Pharmacol* **260:** 177–181, 1994.

61. Bowery B, Rothwell LA and Seabrook GR, Comparison between the pharmacology of dopamine receptors mediating the inhibition of cell firing in rat brain slices through the substantia nigra pars compacta and ventral tegmental area. *Br J Pharmacol* **112:** 873–880, 1994.
62. Liu JC, Cox RF, Greif GJ, Freedman JE and Waszczak BL, The putative dopamine D_3 receptor agonist 7-OH-DPAT: Lack of mesolimbic selectivity. *Eur J Pharmacol* **264:** 269–278, 1994.
63. Patel J, Trout SJ, Palij P, Whelpton R and Kruk Z, Biphasic inhibition of stimulated endogenous dopamine release by 7-OH-DPAT in slices of rat nucleus accumbens. *Br J Pharmacol* **115:** 421–426, 1995.
64. Starr MS and Starr BS, Motor actions of 7-OH-DPAT in normal and reserpine-treated mice suggest involvement of both dopamine D_2 and D_3 receptors. *Eur J Pharmacol* **277:** 151–158, 1995.
65. McElroy JF and Ward KA, 7-OH-DPAT, a dopamine D_3-selective agonist, produces contralateral rotation in 6-hydroxydopamine-lesioned rats. *Drug Dev Res* **34:** 329–335, 1995.
66. Sato K, Ueda H, Okumura F and Misu Y, 6-OHDA-induced lesion of the nigrostriatal dopaminergic neurons potentiates the inhibitory effect of 7-OHDPAT, a selective D_3 agonist, on acetylcholine release during striatal microdialysis in conscious rats. *Brain Res* **655:** 233–236, 1994.
67. Leysen JE, Schotte A, Janssen PMF, Gommeren W, Van Gompel P, Lesage AS, De Backer MD, Luyten WHM, Amlaiky N and Megens AAHP, Interaction of new antipsychotics with neurotransmitter receptors *in vitro* and *in vivo*: Pharmacological to therapeutic significance. In: *Schizophrenia, Alfred Benzon Symposium 38* (Eds. Fog R, Gerlach J and Hemmingsen R), pp. 344–356. Munksgaard, Copenhagen, 1995.
68. Meller E, Bohmaker K, Goldstein M and Basham DA, Evidence that striatal synthesis-inhibiting autoreceptors are dopamine D_3 receptors. *Eur J Pharmacol* **249:** R5–R6, 1993.
69. Meller E, Helmer-Matyjek E, Bohmaker K, Alder CH, Friedhoff AJ and Goldstein M, Receptor reserve at striatal dopamine autoreceptors: Implications for selectivity of dopamine agonists. *Eur J Pharmacol* **123:** 311–314, 1986.
70. Yokoo H, Goldstein M and Meller E, Receptor reserve at striatal dopamine receptors modulating the release of [^{3}H]dopamine. *Eur J Pharmacol* **155:** 323–327, 1988.
71. Cox RF and Waszczak BL, Irreversible receptor inactivation reveals differences in dopamine receptor reserve between A9 and A10 dopamine systems: An electrophysiological analysis. *Brain Res* **534:** 273–282, 1990.
72. Nissbrandt H, Ekman A, Eriksson E and Heilig M, Dopamine D_3 receptor antisense influences dopamine synthesis in rat brain. *Neuroreport* **6:** 573–576, 1995.
73. Pucak ML and Grace AA, Evidence that systemically administered dopamine antagonists activate dopamine neuron firing primarily by blockade of somatodendritic autoreceptors. *J Pharmacol Exp Ther* **271:** 1181–1192, 1994.
74. Lejeune F and Millan MJ, Activation of dopamine D_3 autoreceptors inhibits firing of ventral tegmental dopaminergic neurones *in vivo*. *Eur J Pharmacol* **275:** R7–R9, 1995.
75. Waters N, Lagerkvist S, Lofberg L, Piercey M and Carlsson A, The dopamine D_3 receptor and autoreceptor preferring antagonists (+)-AJ76 and (+)-UH232; A microdialysis study. *Eur J Pharmacol* **242:** 151–163, 1993.
76. Aretha CW, Sinha A and Galloway MP, Dopamine D3-preferring ligands act at synthesis modulating autoreceptors. *J Pharmacol Exp Ther* **274:** 609–613, 1995.
77. Diaz J, Lévesque D, Lammers CH, Griffon N, Martres M-P, Schwartz J-C and Sokoloff P, Phenotypical characterization of neurons expressing the dopamine D_3 receptor in the rat brain. *Neuroscience* **65:** 731–745, 1995.
78. Gobert A, Rivet J-M, Audinot V, Cistarelli L, Spedding M, Vian J, Peglion J-L and Millan MJ, Functional correlates of dopamine D_3 receptor activation in the rat *in vivo* and their modulation by the selective antagonist, (+)-S14297. II. Both D_2 and "silent" D_3 autoreceptors control synthesis and release in mesolimbic, mesocortical and nigrostriatal pathways. *J Pharmacol Exp Ther* **275:** 899–913, 1995.
79. Booth RG, Baldessarini RJ, Marsh E and Owens CE, Actions of (±)-7-hydroxy-*N*,*N*-dipropylaminotetralin (7-OH-DPAT) on dopamine synthesis in limbic and extrapyramidal regions of rat brain. *Brain Res* **662:** 283–288, 1994.
80. Malmberg A, Nordvall G, Johansson AM, Mohell N and Hacksell U, Molecular basis for the binding of 2-aminotetralins to human dopamine D_{2A} and D_3 receptors. *Mol Pharmacol* **46:** 299–312, 1994.
81. Swart PJ, Jansman FG, Drenth BF, de Zeeuw RA, Dijkstra D and Horn AS, Impact of structural differences on the *in vitro* glucuronidation kinetics of potentially dopaminergic hydroxy-2-aminotetralins and naphthoxazines using rat and human liver microsomes. *Pharmacol Toxicol* **68:** 215–219, 1991.
82. Gainetdinov RR, Sotnikova TD, Grekhova TV and Rayevsky KS, Estimation of the interstitial-free concentration of the putative dopamine D_3 receptor-selective agonist 7-OH-DPAT in the dorsal striatum of freely moving rats. *Neurosci Lett* **193:** 65–67, 1995.
83. Waters N, Svensson K, Haadsma-Svensson SR, Smith MW and Carlsson A, The dopamine D3-receptor: A postsynaptic receptor inhibitory on rat locomotor activity. *J Neural Transm Gen Sect* **94:** 11–19, 1993.
84. Svensson K, Carlsson A and Waters N, Locomotor inhibition by the D_3 ligand *R*-(+)-7-OH-DPAT is independent of changes in dopamine release. *J Neural Transm Gen Sect* **95:** 71–74, 1994.
85. Gilbert DB and Cooper SJ, 7-OH-DPAT injected into the accumbens reduces locomotion and sucrose ingestion D_3 autoreceptor-mediated effects. *Pharmacol Biochem Behav* **52:** 275–280, 1995.
86. Svensson K, Johansson AM, Magnusson T and Carlsson A, (+)-AJ76 and (+)-UH232: Central stimulants acting as preferential dopamine autoreceptor antagonists. *Naunyn Schmiedebergs Arch Pharmacol* **334:** 234–245, 1986.
87. Gifford AN and Johnson KM, A pharmacological analysis of the effects of (+)-AJ 76 and (+)-UH 232 at release regulating pre- and postsynaptic dopamine receptors. *Eur J Pharmacol* **237:** 169–175, 1993.
88. Millan MJ, Audinot V, Rivet J-M, Gobert A, Vian J, Prost JF, Spedding M and Peglion J-L, S 14297, a novel selective ligand at cloned human dopamine D_3 receptors, blocks 7-OH-DPAT-induced hypothermia in rats. *Eur J Pharmacol* **260:** R3–R5, 1994.
89. Waters N, Löfberg L, Haadsma-Svensson S, Svensson K, Sonesson C and Carlsson A, Differential effects of dopamine D2 and D3 receptor antagonists in regard to dopamine release, *in vivo* receptor displacement and behaviour. *J Neural Transm Gen Sect* **98:** 39–55, 1994.
90. Millan MJ, Peglion J-L, Vian J, Rivet J-M, Brocco M, Gobert A, Newman-Tancredi A, Dacquet C, Bervoets K, Girardon S, Jacques V, Chaput C and Audinot V, Functional correlates of dopamine D_3 receptor activation in the rat *in vivo* and their modulation by the selective antagonist, (+)-S14927. I. Activation of postsynaptic D_3 receptors mediates hypothermia, whereas blockade of D_2 receptors elicits prolactin secretion and catalepsy. *J Pharmacol Exp Ther* **275:** 885–898, 1995.
91. Millan MJ, Audinot V, Melon C and Newman-Tancredi A,

Evidence that dopamine D_3 receptors participate in clozapine-induced hypothermia. *Eur J Pharmacol* **280:** 225–229, 1995.
92. Sautel F, Griffon N, Sokoloff P, Schwartz J-C, Launay C, Simon P, Costentin J, Schoenfelder A, Garrido F, Mann A and Wermuth CG, Nafadotride, a potent preferential dopamine D_3 receptor antagonist, activates locomotion in rodents. *J Pharmacol Exp Ther* **275:** 1239–1246, 1995.
93. Kling-Petersen T, Ljung E and Svensson K, Effects on locomotor-activity after local application of D_3 preferring compounds in discrete areas of the rat brain. *J Neural Transm Gen Sect* **102:** 209–220, 1995.
94. Caine SB and Koob GF, Modulation of cocaine self-administration in the rat through D_3 dopamine receptors. *Science* **260:** 1814–1816, 1993.
95. Mallet PE and Beninger RJ, 7-OH-DPAT produces place conditioning in rats. *Eur J Pharmacol* **261:** R5–R6, 1994.
96. Caine SB and Koob GF, Pretreatment with the dopamine agonist 7-OH-DPAT shifts the cocaine self-administration dose–effect function to the left under different schedules in the rat. *Behav Pharmacol* **6:** 333–347, 1995.
97. De Fonseca FR, Rubio P, Martin-Calderon JL, Caine SB, Koob GF and Navarro M, The dopamine receptor agonist 7-OH-DPAT modulates the acquisition and expression of morphine-induced place preference. *Eur J Pharmacol* **274:** 47–55, 1995.
98. Smith A, Piercey M and Roberts DCS, Effect of (−)-DS-121 and (+)-UH-232 on cocaine self-administration in rats. *Psychopharmacology* **120:** 93–98, 1995.
99. Suzuki T, Maeda J, Funada M, and Misawa M, The D_3-receptor agonist (±)-7-hydroxy-*N*,*N*-di-*n*-propyl-2-aminotetralin (7-OH-DPAT) attenuates morphine-induced hyperlocomotion in mice. *Neurosci Lett* **187:** 45–48, 1995.
100. Richardson NR, Piercey MF, Svensson K, Collins RJ, Myers JE and Roberts DCS, Antagonism of cocaine self-administration by the preferential dopamine autoreceptor antagonist, (+)-AJ 76. *Brain Res* **619:** 15–21, 1993.
101. Parsons LH, Caine SB, Koob GF and Weiss F, The effects of the D_3 receptor agonist 7-OH-DPAT on cocaine self-administration may be mediated postsynaptically. *Behav Pharmacol* **5** (Suppl 1): 43, 1994.
102. Pulvirenti L and Koob GF, Dopamine receptor agonists, partial agonists and psychostimulant addiction. *Trends Pharmacol Sci* **15:** 374–379, 1994.