ELSEVIER

European Journal of Pharmacology 286 (1995) 223–228

ejp

# Effects of $\sigma$ receptor ligands on the extracellular concentration of dopamine in the striatum and prefrontal cortex of the rat

Gary A. Gudelsky *

*Departments of Psychiatry and Pharmacology, Case Western Reserve University Cleveland, Cleveland, OH 44106, USA*

Received 2 January 1995; revised 28 June 1995; accepted 7 July 1995

**Abstract**

The extracellular concentration of dopamine in the striatum and medial prefrontal cortex of the rat was determined following the systemic administration of $\sigma$ receptor ligands. The (+)-benzomorphan, (+)-pentazocine, significantly increased the extracellular concentration of dopamine in the striatum and medial prefrontal cortex. A stimulatory effect on the extracellular concentration of dopamine in the striatum also was produced by the (+)-, but not the (−)-, enantiomer of *N*-allylnormetazocine, as well as by the non-benzomorphans 1-(cyclopropylmethyl)-4-(2′-(4″-fluorophenyl)-2′-oxoethyl)-piperidine (DUP 734) and (−)-butaclamol. In contrast, the dopamine concentration was unaffected by di-*o*-tolylguanidine and markedly suppressed by (+)-3-[3-hydroxyphenyl]-*N*-(1-propyl)piperidine (3-PPP). Finally, the (+)-pentazocine-induced elevation of the extracellular concentration of dopamine was not suppressed by an inhibitor of the dopamine transporter, 1-[2-[bis(4-fluorophenyl)methoxy]ethyl]-4-[3-phenylpropyl]piperazine (GBR 12909). Thus, benzomorphan, e.g., (+)-pentazocine and (+)-*N*-allylnormetazocine, and non-benzomorphan, e.g., DUP 734 and (−)-butaclamol, $\sigma$ receptor ligands appear to facilitate dopamine release from nigrostriatal, and presumably mesocorticolimbic, neurons through a non-transporter-mediated mechanism.

*Keywords:* (+)-Pentazocine; *N*-Allylnormetazocine; $\sigma$ Receptor; Dopamine; Striatum; Microdialysis

## 1. Introduction

Opiate receptors of the $\sigma$ subtype were initially postulated by Martin et al. (1976) to account for the behavioral effect of racemic, opiate benzomorphans, e.g., (+)-*N*-allylnormetazocine. The term $\sigma$ receptor has replaced $\sigma$ opiate receptor based on the findings that the effects of $\sigma$ receptor ligands are insensitive to naloxone (Young and Khazan, 1986) and that $\sigma$ receptors, in contrast to opiate receptors, exhibit enantioselectivity for the (+)-isomer (Slifer and Balster, 1983).

Data from behavioral studies are supportive of the view that $\sigma$ receptor ligands interact with dopaminergic systems in the central nervous system. The i.c.v. or systemic administration of the $\sigma$ receptor ligand di-*o*-tolylguanidine (DTG) or (+)-*N*-allylnormetazocine has been shown to produce stereotypy and hyperlocomotion (Contreras et al., 1988), similar to that produced by amphetamine. In addition, the intranigral injection of DTG or (+)-pentazocine elicits circling behavior that is suppressed in rats treated with 6-hydroxydopamine (Goldstein et al., 1989).

A neuroanatomical basis for an interaction of $\sigma$ receptors and dopaminergic neurons has been provided by the demonstration of $\sigma$ receptor ligand binding in those brain regions, viz., the striatum and substantia nigra, that contain the terminals and cell bodies, respectively, of nigrostriatal dopamine neurons (Tam and Cook, 1984; Gundlach et al., 1986). Binding sites for $\sigma$ receptor ligands also have been demonstrated in the cortex, in areas containing the terminals of mesocorticolimbic dopamine neurons (Largent et al., 1986; Walker et al., 1992).

Also supportive of the involvement of $\sigma$ receptors in the regulation of dopaminergic neurons are the neurochemical findings of Iyengar et al. (1990) who demonstrated that the (+)-benzomorphans, (+)-pentazocine and (+)-*N*-allyl-normetazocine, increased the

* Present address: College of Pharmacy, University of Cincinnati – Medical Center, 3223 Eden Avenue, Cincinnati, OH 45267-0004, USA. Tel.: (513) 558-5735; fax: (513) 558–4372.

Elsevier Science B.V.
*SSDI* 0014-2999(95)00415-7

concentration of dihydroxyphenylacetic acid (DOPAC) in post mortem samples of the striatum and olfactory tubercle. In addition, (+)-benzomorphans have been shown under in vitro conditions to increase the synthesis of dopamine in slices of the striatum (Booth and Baldessarini, 1992). Furthermore, Patrick et al. (1993) utilized in vivo microdialysis to determine that (+)-pentazocine and DTG increase the extracellular concentration of dopamine in the striatum. Thus, behavioral, neurochemical and neuroanatomical data are supportive of the hypothesis that $\sigma$ receptors modulate dopaminergic neurotransmission in nigrostriatal and, possibly, mesocorticolimbic neurons.

In view of the structural diversity of $\sigma$ receptor ligands, the present study was undertaken to evaluate the effects of $\sigma$ receptor ligands of the benzomorphan type, e.g., (+)-pentazocine and (+)-*N*-allylnormetazocine, and non-benzomorphan type, e.g., 1-(cyclopropylmethyl)-4-(2′-(4″-fluorophenyl)-2′-oxoethyl)-piperidine (DUP 734), (+)-3-[3-hydroxyphenyl]-*N*-(1-propyl)-piperidine ((+)-3-PPP), and (−)-butaclamol, on the release of dopamine from the terminals of nigrostriatal neurons. The effect of one (+)-benzomorphan, (+)-pentazocine, on the release of dopamine from mesocorticolimbic dopaminergic neurons in the medial prefrontal cortex also was determined.

## 2. Materials and methods

### 2.1. Animals

Adult male rats (200–300 g) of the Sprague-Dawley strain (Zivic Miller Laboratories, Allison Park, PA) were used in these studies. The animals were housed three per cage in a temperature-and light-controlled room. Food and water were available ad libitum.

### 2.2. In vivo microdialysis

A concentric style dialysis probe was implanted under chloral hydrate (400 mg/kg, i.v.) anesthesia into the striatum (A: 1.2, L: 3.2, V: −7.5 mm from bregma) or the medial prefrontal cortex (A: 3.5, L: 0.7, V: −4.5 mm from bregma) according to the stereotaxic atlas of Paxinos and Watson (1986). The exposed portion of the membrane for the probes was 4.0 mm. 18–24 h following surgery, the dialysis probes were connected to an infusion pump set to deliver a modified Krebs-Ringer solution (136 mM NaCl, 2.0 mM KCl, 1.2 mM $Ca_2Cl$, 6.0 mM $Na_2HPO_4$, 1.0 mM $KH_2PO_4$, pH 7.4) at 1.8 $\mu$l/min for the striatum and 1.3 $\mu$l/min for the medial prefrontal cortex. After a 2-h equilibration period, dialysis samples were obtained every 30 min. At least four baseline samples were collected prior to drug treatment.

### 2.3. Biochemical measurements

The extracelluar concentration of dopamine was quantified with high performance liquid chromatography with electrochemical detection. Briefly, dialysis samples were injected onto a C18 column (Phenomenex, Torrance, CA) connected to a LC-4B amperometric detector (Bioanalytical Systems, West Lafayette, IN) or a Coulochem detector (ESA, Bedford, MA). The mobile phase consisted of 35 mM citric acid, 54 mM sodium acetate, 60 mg/l of disodium etylenediamine tetraacetate, 65 mg/l of octanesulfonic acid sodium salt, pH 4.2. Peak heights were recorded with an integrator (Model 3396A, Hewlett Packard), and the quantity of dopamine was calculated based on known standards.

### 2.4. Drugs

(+)-Pentazocine succinate and (+)-and (−)-*N*-allylnormetazocine hydrochloride were obtained from the National Institutes of Drug Abuse. (−)-Butaclamol, 1-[2-[bis(4-fluorophenyl)methoxy]ethyl]-4-[3-phenylprpyl]piperazine (GBR 12909) and (+)-3-PPP were purchased from Research Biochemicals (Natick, MA). DTG was purchased from Aldrich Chemical Co (Milwaukee, WI). DUP 734 was provided generously by DuPont Merck Pharmaceutical Co. (Wilmington, DE). The doses of DUP 734, (+)-3-PPP, DTG and (−)-butaclamol were chosen on the basis of earlier reports (Imperato et al., 1988; Iyengar et al., 1990, Rominger and Tam, 1991; Patrick et al., 1993; Hjorth et al., 1985).

### 2.5. Statistics

Data from dialysis experiments were analyzed using a two-way repeated measures analysis of variance (SigmaStat, Jandel Scientific). Multiple pairwise comparisons were performed using the Student Newman-Keuls test. Treatment differences were considered statistically significant at $P < 0.05$.

## 3. Results

The extracellular concentration of dopamine in the striatum was increased dose dependently by (+)-pentazocine (1–20 mg/kg, s.c.) (Fig. 1A). (+)-Pentazocine (10 or 20 mg/kg) produced a significant ($P < 0.05$) increase of approximately 50% in the extracellular concentration of dopamine in the striatum. (+)-Pentazocine (20 mg/kg, s.c.) produced an increase of similar magnitude in the extracellular concentration of dopamine in the medial prefrontal cortex (Fig. 1B). The (+)-pentazocine induced increase in dopamine was 90–120 min in duration.

The enantioselectivity of the (+)-opiate-induced increase in striatal dopamine release also was examined. The administration of (+)-*N*-allylnormetazocine (20 mg/kg, s.c.) elicited an increase in the extracellular concentration of dopamine in the striatum that was similar in magnitude to that produced by (+)-pentazocine (Fig. 2). In contrast, the response to (−)-*N*-allylnormetazocine was significantly less than that produced by the (+)-enantiomer and did not differ significantly from that for vehicle-treated controls.

Extracellular concentrations of dopamine in the striatum also were determined after the administration of non-benzomorphan $\sigma$ receptor ligands. DTG (3 mg/kg, i.p.) did not significantly alter the extracellular concentration of dopamine in the striatum (Fig. 3). Dopamine concentrations also were unaffected by a low dose (0.5 mg/kg) of DTG (data not shown). However, a significant increase in dopamine concentrations was produced by DUP 734 (5 mg/kg, i.p.) (Fig. 3). In addition, a relatively long-lasting increase in the extracellular concentration of dopamine in the striatum was achieved following the administration of (−)-butaclamol (10 mg/kg, i.p.) (Fig. 3). In contrast, (+)-3-PPP (20 mg/kg, i.p.) produced approximately a 80% reduction in the extracellular concentration of dopamine (Fig. 3).

The dopamine response to (+)-pentazocine was examined in rats treated with the dopamine uptake inhibitor GBR 12909, in an attempt to address whether the increase in the extracellular concentration of dopamine elicited by (+)-benzomorphan-type $\sigma$ ligands involved transporter-mediated dopamine release. The administration of (+)-pentazocine (20 mg/kg, s.c.) again produced a 50% increase in the extracellular concentration of dopamine. The administration of GBR

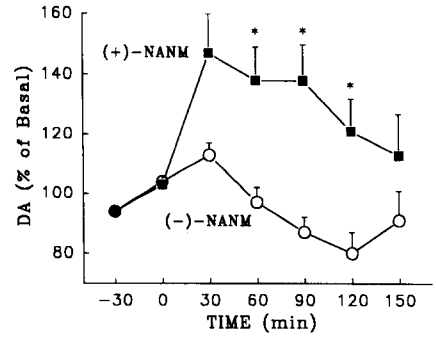


Fig. 2. Enantioselecitivity of the effect of *N*-allylnormetazocine (NANM) on the extracellular concentration of dopamine in the striatum. (+)-or (−)-*N*-allylnormetazocine (20 mg/kg, s.c.) was injected at time 0. Dialysis samples were obtained every 30 min after drug administration. Each symbol and vertical line represent the mean ± S.E.M. of six to eight rats. * Indicates values that differ significantly ($P < 0.05$) from the corresponding value for the (−)-*N*-allylnormetazocine-treated animals.

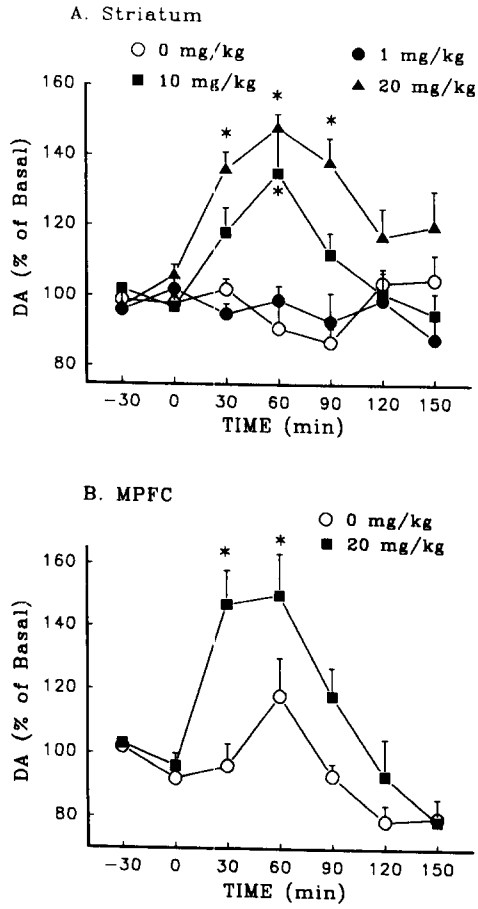


Fig. 1. The effect of (+)-pentazocine on the extracellular concentration of dopamine in the (A) striatum and (B) medial prefrontal cortex (MPFC). (+)-Pentazocine (1, 10 or 20 mg/kg) or its vehicle (0 mg/kg) was injected s.c. at time 0. Dialysis samples were obtained every 30 min after drug administration. Each symbol and vertical line represent the mean ± S.E.M. of 5–11 rats. * Indicates values that differ significantly ($P < 0.05$) from the corresponding value for the vehicle-treated rats.

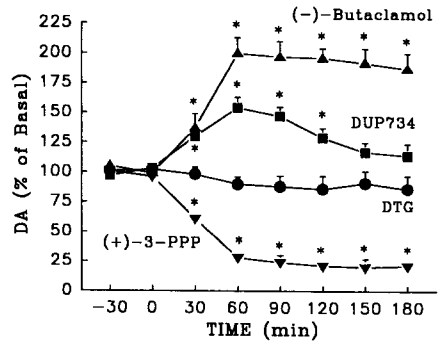


Fig. 3. The effect of DTG, DUP 734, (−)-butaclamol or (+)-3-PPP on the extracellular concentration of dopamine in the striatum. DTG (3 mg/kg, i.p.), DUP 734 (5 mg/kg, i.p.), (−)-butaclamol (10 mg/kg, i.p.) or (+)-3-PPP (20 mg/kg, s.c.) was injected at time 0. The numbers in parentheses represent the doses of each drug. Dialysis samples were obtained every 30 min after drug administration. Each symbol and vertical line represent the mean ± S.E.M. of four to nine rats. * Indicates those values that differ significantly ($P < 0.05$) from the baseline value for each respective group.

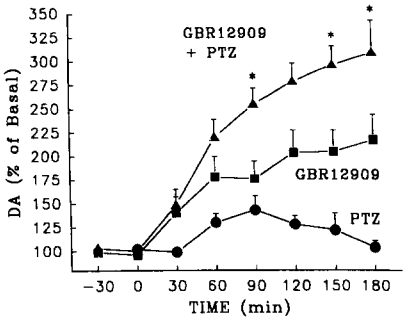


Fig. 4. The effect of GBR 12909 on the (+)-pentazocine-induced elevation of the extracellular concentration of dopamine in the striatum. GBR 12909 (10 mg/kg, i.p.) or its vehicle was injected at time 0. (+)-Pentazocine (PTZ) (20 mg/kg, s.c.) or its vehicle was injected 30 min later. Dialysis samples were obtained every 30 min after drug administration. Each symbol and vertical line represent the mean ± S.E.M. of seven to eight rats. * Indicates values that differ significantly ($P < 0.05$) from the corresponding value for the rats treated with GBR 12909 alone.

12909 (10 mg/kg, i.p.) alone produced approximately a 100% increase in the extracellular concentration of dopamine (Fig. 4). Extracellular concentrations of dopamine in rats treated with both (+)-pentazocine and GBR 12909 were significantly greater than those in rats treated only with GBR 12909 at the 90, 150 and 180 min time periods (Fig. 4). Furthermore, dopamine concentrations in rats treated with (+)-pentazocine and GBR 12909 were significantly greater than those in rats treated only with GBR 12909 at times (i.e., 150 and 180 min) when the dopamine response in rats treated with (+)-pentazocine alone had returned to baseline values.

## 4. Discussion

The results of the present study are consistent with the hypothesis that dopamine release from nigrostriatal neurons is enhanced by (+)-benzomorphan-type, e.g. (+)-pentazocine and (+)-*N*-allylnormetazocine, ligands of the $\sigma$ receptor. This response also is elicited by some non-benzomorphan, e.g., DUP 734 and (−)-butaclamol, ligands of the $\sigma$ site. These findings generally are consistent with those of earlier neurochemical studies in which it had been shown that (+)-pentazocine and (+)-*N*-allylnormetazocine increase the concentration of DOPAC in the striatum (Iyengar et al., 1990) and increase the synthesis of dopamine in striatal slices in vitro (Booth and Baldessarini, 1992). The present fingings confirm and extend those of Patrick et al. (1993) who demonstrated that (+)-pentazocine increases the extracellular concentration of dopamine in the striatum. (+)-Pentazocine also appears to increase the release of dopamine from mesocorticolimbic (A10) dopaminergic neurons, as evidenced by an increase in the extracellular concentration of dopamine in the medial prefrontal cortex. Iyengar and coworkers (Iyengar et al., 1990) also have concluded that $\sigma$ receptor ligands activate A10 dopaminergic neurons on the basis of a (+)-pentazocine-induced increase in DOPAC concentrations in the olfactory tubercle.

On the basis of radioligand binding studies, it is generally accepted that (+)-isomers of benzomorphan-type ligands of the $\sigma$ receptor exhibit a greater affinity for receptors of the $\sigma_1$ subtype compared to $\sigma_2$ receptors, whereas the (−)-enantiomers exhibit an affinity greater than that of the (+)-enantiomer at $\sigma_2$ sites (Quirion et al., 1992). In the present study, the extracellular concentration of dopamine was more effectively increased by (+)-*N*-allylnormetazocine compared to the (−)-enatiomer; (+)-pentazocine also is more effective in this regard (Gudelsky, unpublished observations). This finding is consistent with the relative potencies of the enantiomers of *N*-allylnormetazocine to increase striatal DOPAC concentrations (Iyengar et al., 1990) and is suggestive of the involvement of $\sigma_1$ receptors in the stimulatory effect of these agents on dopamine release.

In view of the affinity of *N*-allylnormetazocine for phencyclidine, as well as $\sigma$ sites (De Costa et al., 1989; Carroll et al., 1992), the possibility that activation of phencyclidine receptors contributes to the stimulatory effect of (+)-*N*-allylnormetazocine on dopamine release cannot be excluded, particularly since phencyclidine also exerts this effect (Lillrank et al., 1994). In view of the differences in affinities of (+)-*N*-allylnormetazocine and (+)-pentazocine for $\sigma$ receptors (Carroll et al., 1992), the near equipotency of these two benzomorphans to stimulate dopamine release is suggestive of a role for mechanisms (i.e., phencyclidine sites) in addition to $\sigma$ receptors in the effect of (+)-*N*-allylnormetazocine. However, an argument that mitigates this possibility is the greater potency of (+)-*N*-allylnormetazocine relative to the (−)-isomer with regard to dopamine release, since the enantiomers exhibit near equal affinities for the phencyclidine receptor (Carroll et al., 1992). Nevertheless, it is conceivable that the actions of (+)-*N*-allylnormetazocine involve both phencyclidine and $\sigma$ receptor mechanisms.

In the present study, DTG, a non-discriminant ligand of $\sigma_1$ and $\sigma_2$ sites, failed to alter the extracellular concentration of dopamine in the striatum. This finding is not in accord with the report of Patrick et al. (1993) who demonstrated that DTG did increase dopamine release in this brain region. The reasons for this discrepancy are not readily apparent. Perhaps noteworthy is the fact that Patrick et al. (1993) utilitzed sodium pentobarbital for surgical procedures, whereas chloral hydrate was used in the present study 24 h prior to beginning dialysis. Chloral hydrate anesthesia has been reported to alter the responsiveness of mid-

brain dopamine neurons (Kelland et al., 1989; Hamilton et al., 1992). A difference in drug preparation also might be a contributory factor. These differences could result in an alteration in the sensitivity of dopamine neurons to DTG. This may be of importance in view of the fact that DTG can exhibit complex, bell shaped dose-effect relationships in some experimental paradigms (Bergeron et al., 1994; Earley et al., 1991).

DUP 734 exhibits high affinity for $\sigma$ and 5-$HT_2$ receptors (Tam et al., 1992) and has been reported to increase DOPAC concentrations in the prefrontal cortex, as well as the striatum (Rominger and Tam, 1991). The stimulatory effect of DUP 734 on the extracellular concentration of dopamine in the striatum in the present study is consistent with this latter finding. DUP 734 has been characterized as a $\sigma$ receptor 'antagonist' (Tam et al., 1992), and it is noteworthy that other putative $\sigma$ receptor 'antagonists', e.g., BMY 14802 and remoxipride, also increase the extracellular concentration of dopamine in the striatum (Gudelsky and Nash, 1992). There is considerable controversy regarding the classification of the $\sigma$ receptor ligands used in the present study as agonists or antagonists. In many instances, the pharmacology of these agents seems to be specific for the particular biological response that is being evoked. The similarity of action on dopamine release of the $\sigma$ receptor ligands tested, with the exception of (+)-3-PPP, seemingly precludes the use of the terms agonist or antagonist with regard to this response.

Although (+)-3-PPP exhibits high affinity for $\sigma$ receptors (De Costa et al., 1989), it also exhibits considerable affinity for dopamine receptors (Sonesson et al., 1992). The biochemical, electrophysiological, and neuroendocrinological effects of (+)-3-PPP are similar to those exerted by dopamine agonists (Clark et al., 1985; Steinfels et al., 1989; Iyengar et al., 1991; Mikuni et al., 1984). The inhibitory effect of (+)-3-PPP on the extracellular concentration of dopamine in the present study is in accord with previous findings (Imperato et al., 1988; Svensson et al., 1994) and is consistent with a dopamine agonist property of the drug.

Although the (+)-enantiomer of butaclamol has high affinity for dopamine receptors (Seeman, 1980) and exerts anti-dopaminergic effects (Hjorth et al., 1985), there is little evidence to suggest that the (−)-butaclamol-induced elevation of the extracellular concentration of dopamine is due to an effect at dopamine receptors. (−)-Butaclamol has little affinity for dopamine receptors (Seeman, 1980), and Hjorth et al. (1985) have shown that (−)-butaclamol is inactive in behavioral, biochemical and hormonal tests for dopamine antagonist properties. Thus, it would seem that the stimulatory effect of (−)-butaclamol on striatal dopamine release is related to its high affinity for the $\sigma$ receptor.

Inhibitors of dopamine uptake, such as mazindol, GBR 12909 and nomifensine, have been shown to suppress dopamine release induced by amphetamine or 3,4-methylenedioxymethamphetamine (Nash and Brodkin, 1991; Butcher et al., 1988; Hurd and Ungerstedt, 1989). Blockade of drug-induced dopamine release by inhibitors of the dopamine transporter has been viewed as evidence in support of the conclusion that such drugs, i.e., amphetamine, facilitate dopamine release through a carrier-or transporter-mediated mechanism. In the present study, GBR 12909 did not suppress the stimulatory effect of (+)-pentazocine on extracellular concentrations of dopamine in the striatum; indeed, at times, the response to (+)-pentazocine was enhanced. Thus, it seems reasonable to conclude that the stimulatory effect of these $\sigma$ receptor ligands on dopamine release does not involve facilitation of transporter-mediated dopamine release. Inasmuch as it is generally believed that dopamine release may occur through either carrrier-mediated or impulse-dependent mechanisms (Seiden et al., 1993), it is tempting to speculate that the stimulation of dopamine release by $\sigma$ receptor ligands is an impulse dependent process.

## Acknowledgements

This work was supported by USPHS MH 49628 and MH 41684. The excellent technical assistance of Mr. Wenjun Zhu is gratefully acknowledged.

## References

Bergeron, R., C. DeMontigy and G. Debonnel, 1994, Biphasic effects of sigma ligands on the neuronal response to *N*-methyl-D-aspartate, Naunyn-Schmied. Arch. Pharmacol. 352, 252.

Booth, R. and R.J. Baldessarini, 1992, (+)-6,7-Benzomorphan sigma ligands stimulate dopamine synthesis in rat corpus striatum tissue, Brain Res. 557, 349.

Butcher, S.P., I.S. Fairbrother, J.S. Kelly and G.W. Arbuthnutt, 1988, Amphetamine-induced dopamine release in the rat striatum: an in vivo microdialysis study, J. Neurochem. 50, 346.

Carroll, F.I., P. Abraham, K. Parham, X. Bai, X. Zhang, G. Brine, X. Mascarella, B. Martin, E. May, C. Sauss, L. Di Paolo, P. Wallace, J.M. Walker and W.D. Bowen, 1992, Enantiomeric *N*-substituted normetazocines: a comparative study of affinities at $\sigma$, PCP, and $\mu$ opioid receptors, J. Med. Chem. 35, 2812.

Clark, C., S. Hjorth and A. Carlsson, 1985, Dopamine-receptor agonists: mechanisms underlying autoreceptor selectivity I. Review of the evidence, J. Neural Transm. 62, 1.

Contreras, P.C., M.L. Contreras, T.L. O'Donohue and C.C. Lair, 1988, Biochemical and behavioral effects of sigma and PCP ligands, Synapse 2, 240.

De Costa, B., W.D. Bowen, S. Hellewell, J.M. Walker, A. Thurkauf, A. Jacobson and K. Rice, 1989, Synthesis and evaluation of optically pure $^3$H-(+)-pentazocine, a highly potent and selective radioligand for $\sigma$ receptors, FEBS Lett. 251, 53.

Earley, B., M. Burke, B.E. Leonard, C. Gouret and J.L. Junien, 1991, Evidence for an anti-amnesic effect of JO-1784 in the rat: a potent and selective ligand for the sigma receptor, Brain Res. 546, 282.

Goldstein, S.R., R.R. Matsumoto, T.L. Thompson, R. Patrick, W.D. Bowen and J.M. Walker,1989, Motor effects of two sigma ligands mediated by nigrostriatal dopamine neurons, Synapse 4, 254.

Gudelsky, G.A. and J.F. Nash, 1992, Neuroendocrinological and neurochemical effects of sigma ligands, Neuropharmacology 31, 157.

Gundlach, A.L., B.L.Largent and S.H. Snyder, 1986, Autoradiographic localization of $\sigma$-receptor binding sites in guinea pig and rat central nervous system with (+)-$^3$H-3-(3-hydroxyphenyl)*N*-(1-propyl)-piperidine, J Neurosci. 6, 1757.

Hamilton, M.E., A. Mele and A. Pert, 1992, Striatal extracellular dopamine in conscious vs. anesthetized rats: effects of chloral hydrate anesthetic on responses to drugs of different classes, Brain Res. 597, 1.

Hjorth, S., D. Clark and A. Carlsson, 1985, Lack of functional evidence for the involvement of sigma opiate receptors in the actions of the 3-PPP enantiomers on central dopaminergic systems: discrepancies between in vitro and in vivo observations, Life Sci. 37, 673.

Hurd, Y.L. and U. Ungerstedt, 1989, $Ca^{2+}$ dependence of the amphetamine, nomifensine and LU 19-005 effect on in vivo dopamine transmission, Eur. J. Pharmacol. 166, 261.

Imperato, A., G. Tanda, R. Frau and G. DiChiara, 1988, Pharmacological profile of dopamine receptor agonists as studied by brain dialysis in behaving rats, J. Pharmacol. Exp. Ther. 245, 257.

Iyengar, S., V. Dilworth, S. Mick S, P.C. Contreras, J. Monahan, T. Rao and P.L. Wood, 1990, Sigma receptors modulate A9 and A10 dopaminergic neurons in the rat brain: functional interaction with NMDA receptors, Brain Res. 524, 322.

Iyengar, S., P.L. Wood, S. Mick, V. Dilworth, N. Gray, J. Farah, T. Rao and P.C. Contreras, 1991, (+)-3-{3-Hydroxyphenyl-*N*-(1-propyl) piperidine selectivey differentiates effects of sigma ligands on neurochemical pathways modulated by sigma receptors: evidence for subtypes in vivo, Neuropharmacology 30, 915.

Kelland, M., A. Freeman and L. Chiodo, 1989, Chloral hydrate anesthesia alters the responsiveness of identified midbrain dopamine neurons to dopamine agonist administration, Synapse 3, 30.

Largent, B., A. Gundlach and S. Snyder, 1986, Pharmacological and autoradiographic discrimination of sigma and phencyclidine receptor binding sites in brain with (+)-[$^3$H]-SKF 10047, (+)-[$^3$H]-3-[3-hydroxyphenyl]-*N*-(1-propyl)piperidine and [$^3$H]-1-[1-(2-thienyl)cyclohexyl]piperidine, J. Pharmacol. Exp. Ther. 238, 739.

Lillrank, S., W.T. O'Connor, S.S. Oja and U. Ungerstedt, 1994, Systemic phencyclidine administration is associated with increased dopamine, GABA, and 5-HIAA levels in the dosolateral striatum of conscious rats: an in vivo microdialysis study, J. Neural Transm. 95, 145.

Martin, W.R., C.Eades, J. Thompson and R. Huppler, 1976, The effects of morphine-and naloerphine-like drugs in the non-dependent and morphine-dependent chronic spinal dog, J. Pharmacol. Exp. Ther. 197, 517.

Mikuni, M., G.A. Gudelsky, M. Simonovic and Meltzer, H.Y., 1984, Interaction of (+)-and (−)-3-PPP with the dopamine receptor in the anterior pituitary gland, Life Sci. 34, 239.

Nash, J.F. and J. Brodkin, 1991, Microdialysis studies on 3,4-methylenedioxy-methamphetamine-induced dopamine release: effect of dopamine uptake inhibitors, J. Pharmacol. Exp. Ther. 259, 820.

Patrick, S.L., J.M. Walker, J. Perkel, M. Lockwood and R.L. Patrick, 1993, Increases in rat striatal extracellular dopamine and vacuous chewing produced by two sigma ligands, Eur. J. Pharmacol. 231, 243.

Paxinos, G. and C. Watson, 1986, The Rat Brain in Stereotaxic Coodinates (Academic Press, New York).

Quirion, R., W.D. Bowen, Y. Itzhak, J. Junien, J. Masacchio, R. Rothman, T.-P. Su, S. W. Tam and D. Taylor, 1992, A proposal on the classification of sigma binding sites, Trends Pharmacol. Sci. 13, 85.

Rominger, C. and S.W. Tam, 1991, The novel antipsychotic DUP 734 preferentially increased dopamine turnover in the frontal cortex in rat brains, Abstr. Soc. Neurosci. 17, 333.

Seeman, P., 1980, Brain dopamine receptors, Pharmacol. Rev. 32, 229.

Seiden, L., K. Sabol and G. Ricaurte, 1993, Amphetamine: effects on catecholamine systems and behavior, Ann. Rev. Pharmacol. Toxicol. 32, 639.

Slifer, B.L. and R. Balster, 1983, Reinforcing properties of stereoisomers of the putative $\sigma$ agonist *N*-allyl-normetazocine and cyclazocine in rhesus monkeys, J. Pharmacol. Exp. Ther. 225, 522.

Sonesson, C., N. Waters, K. Svensson, A. Carlsson, M. Smith, M. Piercey, E. Meier and H. Wikstrom, 1992, Substituted 3-phenylpiperidines: new centrally acting dopamine autoreceptor antagonists, J. Med. Chem. 36, 3188.

Steinfels, G., S.W. Tam and L. Cook, 1989, Electrophysiological effects of selective $\sigma$ receptor agonists, antagonists and the selective phencyclidine receptor agonist MK-801 on midbrain dopamine neurons, Neuropsychopharmacology 2, 201.

Svensson, K., A. Carlsson, R. Huff, T. Kling-Petersen and N. Waters, 1994, Behavioral and neurochemical data suggest functional differences between dopamine $D_2$ and $D_3$ receptors, Eur. J. Pharmacol. 263, 235.

Tam, S.W. and L. Cook, 1984, $\sigma$-Opiates and certain antipsychotic drugs mutually inhibit (+)-[$^3$H]haloperidol binding in guinea pig brain membranes, Proc. Natl. Acad. Sci. 81, 5618.

Tam, S.W., G.F. Steinfels, P.J. Gilligan, W. Schmidt and L. Cook, 1992, DUP 734 [1-(cyclopropylmethyl)-4-(2′-(4″-flurorphenyl)-2′-oxoethyl)peiperidine HBr], a sigma and 5-hydroxytryptamine2 receptor antagonist: receptor binding, electrophysiological and neuropharmacological profiles, J. Pharmacol. Exp. Ther. 263, 1167.

Walker, J.M., W.D. Bowen, S.R. Goldstein, A.H. Roberts, S.L. Patrick, A. G. Hohmann and B. DeCosta, 1992, Autoradiographic distribution of [$^3$H](+)-pentazocine and [$^3$H]1,3-di-*o*-tolylguanidine (DTG) binding sites in guinea pig brain: a comparative study, Brain Res. 581, 33.

Young, G.A. and N. Khazan, 1986, Differential neuropharmacological effects of mu, kappa and sigma opioid agonists on cortical EEG power spectra in the rat-stereospecificity and naloxone antagonism, Neuropharmacology 23, 1161.