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Influence of Dopaminergic and Noradrenergic Systems on the Release of Opioid Peptides in Guinea-pig Ileum

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Abstract—Neuroleptic drugs increase the biosynthesis and release of opioid peptides from the myenteric plexus of guinea-pig ileum. In the present work, the involvement of dopamine receptors or α-adrenoceptors in the release of opioids from the myenteric plexus of guinea-pig was investigated. Acute or chronic treatment with prazosin, an α_1-blocking drug, produced no changes in the release of these peptides. Release was also unchanged after acute or chronic treatment with the α_2-blocking drug yohimbine. However, treatment with domperidone, a selective dopamine receptor antagonist, resulted in an increase in the release of opioids, as did treatment with (-)-3-(3-hydroxyphenyl)-*N*-n-propylpiperidine ((–)-3-PPP), a dopamine autoreceptor stimulant. It is concluded that the effect of neuroleptics on the release of opioids from myenteric plexus is due to the blockade of dopamine receptors, and that interruption of dopaminergic transmission produces an increase in opioid release at this level.

The myenteric plexus of guinea-pig contains a variety of opioid peptides (Furness et al 1983; Vincent et al 1984). Although the chemical nature and biosynthetic pathways of these systems have been identified, little is known concerning the regulatory mechanisms of the myenteric plexus opioid peptides.

Considerable evidence suggests that a dopaminergic system in several regions of the brain modulates the synthesis and release of endogenous opioid peptides (Palmer et al 1983; Hong et al 1985). It has been reported that dopamine (DA) plays a role in regulating the metabolism of met-enkephalin- (Sabol et al 1983; Thal et al 1983; Blanc et al 1985; Angulo et al 1986) and dynorphin-containing neurons (Quirion et al 1985; Li et al 1986) in the striatum. We have suggested that opioid peptide synthesis in the myenteric plexus of guinea-pig is also under modulation by a similar system. In support of this hypothesis are our recent observations (Milanés et al 1984, 1985; Vargas et al 1987) that treatment with neuroleptics, such as haloperidol, sulpiride, clozapine or droperidol, increases the biosynthesis and release of opioid peptides from the myenteric plexus of guinea-pig ileum. Moreover, interruption of dopaminergic neuronal transmission by stimulation of DA autoreceptors or after treatment with 6-hydroxydopamine also resulted in an increase in the release of these peptides (Vargas et al 1986). These observations suggest a possible functional relationship between DA and opioid systems at that level. However, in addition to being DA antagonists, all antipsychotic drugs are antagonists of α-noradrenergic receptors (Hornykiewicz 1982; Richelson & Nelson 1984), and the possible contribution of α-blocker to the effect of these drugs on the release of opioid peptides must not be discarded.

The present study was designed to analyse (i) whether noradrenergic blockers alter the release of these peptides from the myenteric plexus of guinea-pig ileum; (ii) the effect of selective DA receptor blockers or selective activation of DA autoreceptors, on the release of opioid peptides. The myenteric plexus-longitudinal muscle (MPLM) strip was used as the source of opioid peptides.

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Materials and Methods

MPLM preparation

Guinea-pigs of either sex, 300–450 g, were stunned and decapitated. The abdomen was opened, the terminal ileum removed and the last 15 cm discarded routinely. To remove the intestinal contents, the lumen of the ileum was washed with Krebs solution which consisted of (mM): NaCl, 118; KCl, 4·7; $CaCl_2$, 2·5; $NaHCO_3$, 25; $MgCl_2$, 1·2; NaH_2PO_4, 1·2; glucose, 11. Segments 3 cm long were freed and the MPLM strips were obtained by the method of Kosterlitz et al (1970). Each strip was suspended in a 2 mL organ bath containing Krebs solution at 37°C, bubbled with 95% O_2 and 5% CO_2. The preparation was suspended under a resting tension of 0·3 g and allowed to equilibrate for 45 min, while the strip was washed every 15 min with Krebs solution. The strip was then electrically stimulated by a Grass stimulator by means of two platinum ring electrodes, placed at the top and bottom of the organ bath, with rectangular pulses at a frequently of 0·2 Hz, duration 1 ms and supramaximal voltage (40V) to produce contractions of the longitudinal muscle. Contractions were registered by a Statham force transducer coupled to a Dynograph Beckman Polygraph recorder. To produce an opioid-like inhibition of the contractions, the frequency of stimulation was increased to 10 Hz for 30 s, and when the basal frequency was resumed, an inhibitory response (IR) appeared, which was reversed by naloxone. The main component of this response is due to the endogenous opioid peptide release (Puig et al 1977), on the basis of its reversal by naloxone. Periods of stimulation at 10 Hz for 30 s were repeated five times every 30 min, and 0·01 mL naloxone (5×10^{-7}M) was added to the bath 5 min before the last stimulation.

Quantitation of the inhibitory response (IR) and its reversal by naloxone

The IR and its reversal by naloxone were calculated as follows (Puig et al 1977): The area of the recorder contractions generated in 5 min by stimulation at 0·2 Hz was measured before (basal response, BR) and immediately after stimulation at 10 Hz (post-stimulation response, PSR). The percent IR was calculated as $((BR-PSR)/BR) \times 100$. The antagonism of the IR by naloxone, represented as the percentage reversal, was calculated as follows: $\%\ \text{reversal} = ((\%\ IR_c - \%IR_e)/\%IR_c) \times 100$, where IR_c is the IR of the control and IR_e is the IR in the presence of naloxone.

Treatment groups

The four treatment groups were:

(i) *Treatment with prazosin.* (a) *Acute treatment.* Guinea-pigs were injected with prazosin (0·1 mg kg^{-1}) or vehicle intraperitoneally (i.p.) and decapitated 2 h later. (b) *Chronic treatment.* Animals were treated for 4 days with daily injections of prazosin (0·1 mg kg^{-1}) or vehicle i.p. and were killed 12 h after the last injection. Prazosin was dissolved in a few drops of 0·1 M HCl and diluted with saline.

(ii) *Treatment with yohimbine.* (a) *Acute treatment.* Guinea-pigs were injected with yohimbine (0·5 mg kg^{-1}) or saline i.p. and killed 2 h later. (b) *Chronic treatment.* Guinea-pigs were treated for 4 days with daily injections of yohimbine (0·5 mg kg^{-1}) or saline i.p. and were killed 12 h after the last injection.

(iii) *Treatment with domperidone.* Domperidone (15 mg kg^{-1}) or vehicle were injected i.p. twice daily for 7 days. Guinea-pigs were killed 12 h after the last injection. Domperidone was dissolved in 0·9% NaCl (saline) containing 1% tartaric acid.

(iv) *Treatment with (−)-3-(3-hydroxyphenyl)-N-n-propylpiperidine, ((−)-3-PPP).* Guinea-pigs were treated for 4 days with daily injections of (−)-3-PPP (5 mg kg^{-1}) or saline subcutaneously (s.c.) and killed 12 h after the last treatment.

The doses of prazosin and yohimbine were chosen since they have been shown to be effective in producing α_1- and α_2-adrenoceptor blockade, respectively (Van Meel et al 1981; Kobinger & Pichler 1981; Hsu et al 1986). The dose of domperidone was decided on the basis of its pharmacological and pharmacokinetic features (Brogden et al 1982; Champion et al 1986). The dose of (−)-3-PPP was selected to be effective in activating the DA autoreceptors selectively (Hjorth et al 1981, 1985).

Drugs

The drugs used were: domperidone (Esteve, Barcelona, Spain); (−)-3-PPP hydrochloride (Astra, Södertälje Sweden); prazosin hydrochloride (Pfizer, New York, USA); yohimbine hydrochloride (Leo, Madrid, Spain); naloxone hydrochloride (Abelló, Madrid, Spain). Drug doses were calculated as salts.

Statistical analysis

Results were expressed as the mean of n experiments ± s.e.m. Inhibitory responses were analysed by two-way analysis of variance (ANOVA) with Student's *t*-test for individual comparison. Reversal by naloxone was evaluated using Student's *t*-test. A P value less than 0·05 was considered significant.

Results

Effect of adrenergic α_1-antagonism on the inhibitory response

Fig. 1A shows the effect of the α_1-blocking agent prazosin (0·1 mg kg^{-1}) administered to the guinea-pigs 2 h before death. The inhibitory response was 51·42 ± 0·8%, which was not significantly different from that of the control (49·05 ± 1·5%). In the presence of naloxone the response was reversed in both groups, being 55·35 ± 4·3% in the prazosin-treated animals and 49·79 ± 6·4% in the control group.

When guinea-pigs were treated with the same dose of prazosin for 4 days, there was no significant difference in the response obtained with the drug (39·18 ± 1·3%) or with the vehicle (42·27 ± 1·1%). The reversal by naloxone was 46·18 ± 8·9% in the prazosin-treated group and 46·78 ± 5% in the control group (Fig. 1B).

Effect of adrenergic α_2-antagonism on the inhibitory response

The inhibitory response obtained when guinea-pigs were injected with yohimbine (0·5 mg kg^{-1}) 2 h before death (50·65 ± 0·8%) was not significantly different from that

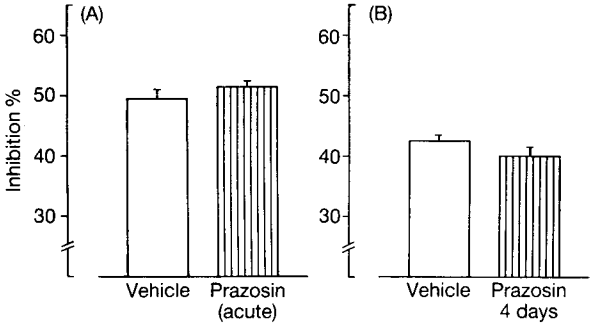

FIG. 1. Percent inhibitory responses of the MPLM preparation elicited by stimulation at 10 Hz when guinea-pigs were injected with vehicle or prazosin (0·1 mg kg^{-1} i.p.) 2 h before death (A) and when guinea-pigs were treated with vehicle or prazosin (0·1 mg kg^{-1} i.p.) for 4 days (B) (mean ± s.e.m., n = 5–10).

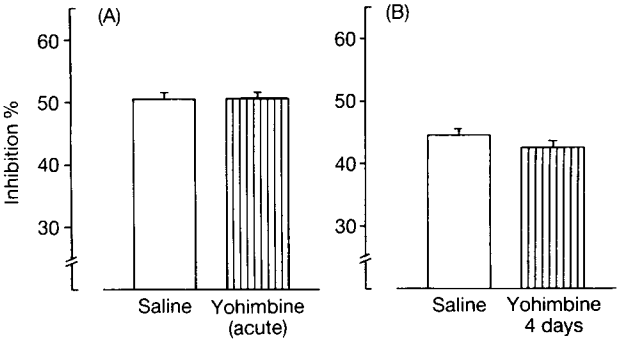

FIG. 2. Percent inhibitory responses elicited by stimulation at 10 Hz of the MPLM preparation when guinea-pigs received saline or yohimbine (0·5 mg kg^{-1} i.p.) 2 h before death (A) and when guinea-pigs were treated with saline or yohimbine (0·5 mg kg^{-1} i.p.) for 4 days (B) (mean ± s.e.m., n = 5–8).

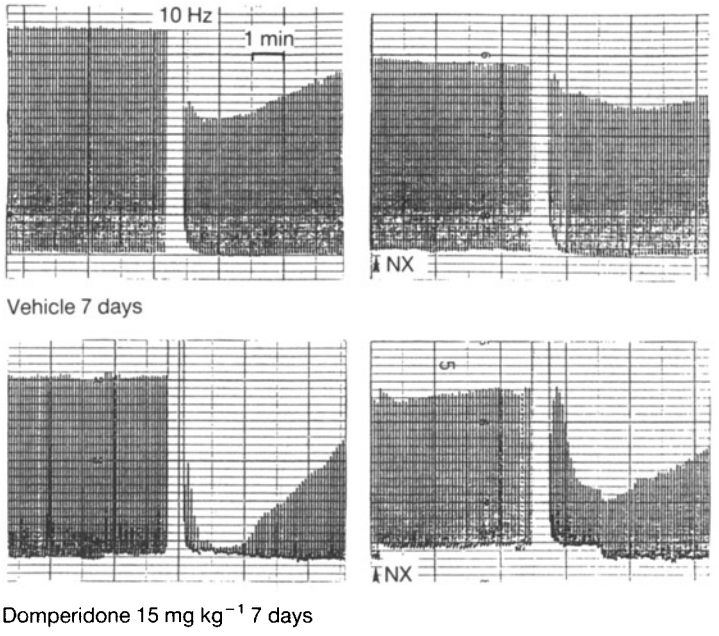

FIG. 3. Examples of the inhibitory responses (left) elicited by stimulation at 10 Hz of the MPLM strip and reversal by naloxone 5×10^{-7} M (right) when guinea-pigs were treated for 7 days with vehicle or domperidone 15 mg kg^{-1} i.p.

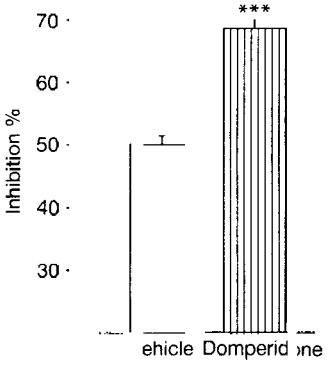

FIG. 4. Percent inhibitory responses elicited by stimulation at 10 Hz of MPLM strip when guinea-pigs were treated for 7 days with vehicle (open column) or domperidone 15 mg kg^{-1} i.p. (hatched column). Each value is the mean of 10 experiments. The s.e.m. is indicated. ***Significantly different from corresponding control value ($P < 0.001$, two-way analysis of variance).

obtained in the control group (50·60 ± 0·9%). In the presence of naloxone, the response was reversed in both groups, being 52·26 ± 4% in the yohimbine-treated group and 52·03 ± 7·5% in the control group (Fig. 2A).

Treatment with daily injections of yohimbine (0·5 mg kg^{-1}) for 4 days produced a response of 42·51 ± 0·9%, which was not significantly different from the inhibitory response obtained in the control group (44·49 ± 0·9%). The reversal of the response by naloxone was 44·76 ± 4·0% in the yohimbine-treated animals and 37·02 ± 9·0% in the control group (Fig. 2B).

Treatment with domperidone

Administration of domperidone, a selective DA antagonist (Laduron & Leysen 1979; Kohli et al 1983), 15 mg kg^{-1} twice daily over 7 days, caused a significantly higher ($P < 0.001$) inhibitory response than that obtained with the vehicle-injected group (Figs 3,4). The response was 68·63 ± 2·0% in the domperidone-treated animals and 49·85 ± 1·2% in the control group. Naloxone produced a reversal of the inhibitory response in domperidone-treated and control groups, being 55·49 ± 2·4% and 47·85 ± 4·7%, respectively ($P < 0.01$).

Treatment with (−)-3-PPP

Treatment of guinea-pigs with (−)-3-PPP (5 mg kg^{-1}), a selective DA autoreceptor agonist (Hjorth et al 1981), produced an inhibitory response of 62·00 ± 1·2%, which was significantly higher ($P < 0.001$) than that obtained in the control group (44·49 ± 0·9%) (Figs 5,6). In the presence of naloxone, the response was reversed in both groups, being 55·00 ± 6·0% in the group treated with this drug and 37·02 ± 9·0% in the control group ($P < 0.001$).

In an isolated test, acute injections of domperidone (15 mg, kg^{-1} i.p.) of (−)-3-PPP (5 mg kg^{-1} s.c.) did not produce a significant variation in the response.

Discussion

In previous studies, treatment with classic or atypical neuroleptics was found to consistently increase the biosynthesis and release of opioid peptides from the myenteric plexus of guinea-pig ileum (Milanés et al 1984, 1985; Vargas et al 1987), and it was proposed that opioid neurons at that level were under modulation by dopaminergic systems. However, all neuroleptics have some antagonist action on α-noradrenoceptors (Hornykiewicz 1982; Richelson & Nelson 1984; Cohen & Lipinski 1986). Therefore the possible increase in the release of opioids from the myenteric plexus due to α-noradrenoceptor blockade has been investigated.

Acute treatment with prazosin produced an inhibitory

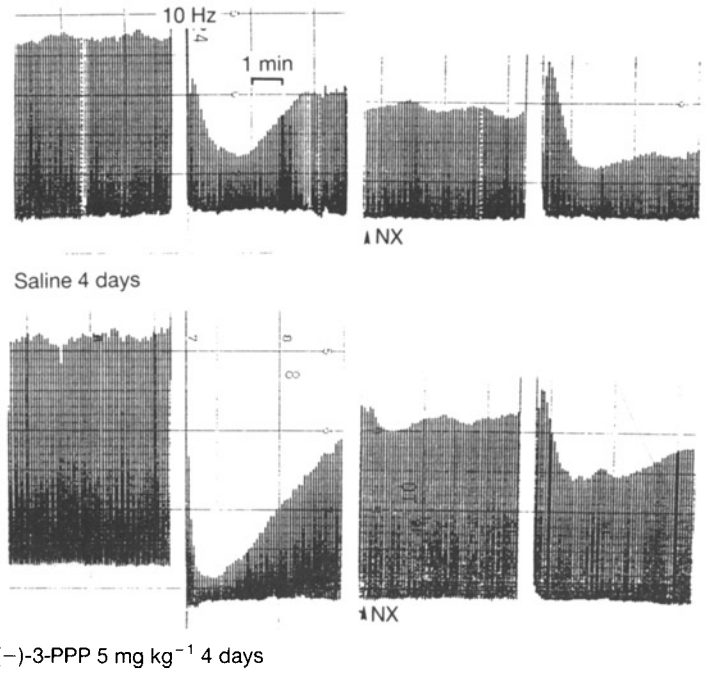

FIG. 5. Examples of the inhibitory responses (left) elicited by stimulation at 10 Hz of the MPLM preparation and reversal by naloxone 5×10^{-7} M (right) when--guinea-pigs received saline or (−)-3-PPP 5 mg kg^{-1} i.p. for 4 days.

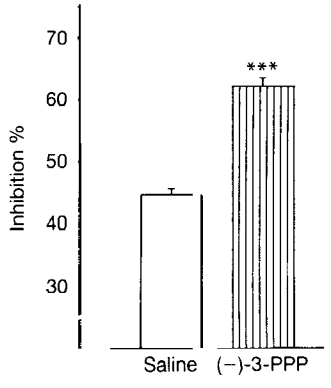

FIG. 6. Percent inhibitory response elicited by stimulation at 10 Hz of MPLM preparation when guinea-pigs were treated for 4 days with saline (open column) or (−)-3-PPP 5 mg kg^{-1} i.p. (hatched column). Each value is the mean ± s.e. from 5–8 experiments. *** Significantly different from control value ($P < 0.001$, two-way analysis of variance).

response that was not significantly different from the response obtained in vehicle-treated guinea-pigs. Likewise, the inhibitory response was unchanged after the four day prazosin treatment. These results show that the blockade of α_1-receptors did not alter the release of opioid peptides after high frequency electrical stimulation of the MPLM strip.

Acute or chronic treatment of guinea-pigs with yohimbine produced no changes in the inhibitory response, which would seem to indicate that α_2-blockade did not modify the release of these peptides. The timing of the treatment with prazosin or yohimbine was identical to the time of administration of haloperidol from previous work (Milanés et al 1984). These results suggest that the increase of biosynthesis and release of opioid peptides induced by neuroleptics in the myenteric plexus of guinea-pigs is exclusively due to the blockade of DA receptors produced by these drugs.

The action of DA and DA antagonists in the gastrointestinal tract has been suggested to be via receptors other than DA receptors (Costall et al 1983; Fernández & Massingham 1985). However, it has been demonstrated that DA and DA antagonists can modulate gastrointestinal motility via direct action on DA receptors at that level. Thus, the inhibitory effect of DA on gastrointestinal motility is reversed by specific DA antagonists (Van Nueten & Schuurkes 1984; Schuurkes & Van Nueten 1984). Furthermore, phentolamine (an α-antagonist), prazosin (an α_1-antagonist), yohimbine (an α_2-antagonist) and propranolol (a β-antagonist) did not affect the inhibitory effect of DA on acetylcholine release from guinea-pig stomach. However, treatment with haloperidol, sulpiride or domperidone did inhibit this DA effect (Kusunoki et al 1985).

The existence of a modulation of opioid peptides by DA systems in the myenteric plexus is further suggested by the effect obtained after treatment with domperidone, a selective DA receptor blocker (Laduron & Leysen 1979; Kohli et al 1983), which resulted in an increase in the release of these peptides. Although the existence of DA neurons in the alimentary tract is still under discussion, recent findings suggest that there are dopaminergic nerves and specific DA receptors at this level (Hernández et al 1984; Van Nueten & Schuurkes 1984; Kusunoki et al 1985; Orloff et al 1985). The present data agree and support the hypothesis that DA is present in the enteric nervous system.

Previously (Vargas et al 1986), we have found that stimulation of DA autoreceptors with appropriate doses of apomorphine or bromocryptine produces an increase in the release of opioids from the myenteric plexus of the guinea-pig. In the present work, treatment with (−)-3-PPP, a

selective DA autoreceptor stimulant (Hjorth et al 1981), also produced an increase in the release of these peptides. According to the DA autoreceptor hypothesis, which postulates that DA autoreceptors have an inhibitory role on DA synthesis and release (Skirboll 1979), we suggest that the increase in opioids released after (-)-3-PPP treatment is due to the interruption of DA release induced by this drug.

These results might reflect the existence of a dynamic balance between a DA system and opioid peptides in the myenteric plexus of the guinea-pig ileum. Since both DA and opioids have an inhibitory effect on acetylcholine release in gastrointestinal tract (Kusunoki et al 1985), we expect that interruption of DA neural transmission could produce a compensatory increase in the release of opioids at that level.

References

Angulo, J. A., Davis, L. G., Burkhart, B. A., Christoph, G. R. (1986) Reduction of striatal dopaminergic neurotransmission elevates striatal proenkephalin mRNA. Eur. J. Pharmacol. 130: 341–343

Blanc, D., Cupo, A., Castanas, E., Bourhim, N., Giraud, P., Bannon, M. J., Eiden, L. E. (1985) Influence of acute, subchronic and chronic treatment with neuroleptic (haloperidol) on enkephalins and their precursors in the striatum of rat brain. Neuropeptides 5: 567–570

Brogden, R. N., Carmine, A. A., Heel, R. C., Steight, T. N., Avery, G. S. (1982) Domperidone: a review of its pharmacological activity, pharmacokinetics and therapeutic efficacy in the symptomatic treatment of chronic dyspepsia and as antiemetic. Drugs 24: 360–400

Champion, M. C., Hartnett, M., Yen, M. (1986) Domperidone, a new dopamine antagonist. CMAJ 135: 457–461

Cohen, B. M., Lipinski, J. F. (1986) In vivo potencies of antipsychotic drugs in blocking alpha-1 noradrenergic and dopamine D_2 receptors: Implications for drug mechanism of action. Life Sci. 39: 2571–2580

Costall, B., Naylor, R. I., Tan, C. W. (1983) Field stimulation-induced responses of circular muscle from guinea-pig stomach. Naunyn-Schmiedeberg's. Arch. Pharmacol. 323: 155–161

Fernández, A. G., Massingham, R. (1985) Peripheral receptor populations involved in the regulation of gastrointestinal motility and the pharmacological actions of metoclopramide-like drugs. Life Sci. 36: 1–14

Furness, J. B., Costa, M., Miller, R. J. (1983) Distribution and projections of nerves with enkaphalin-like immunoreactivity in the guinea-pig small intestine. Neuroscience 8: 653–664

Hernández, D. E., Adcock, J. W., Orlando, R. C., Patrick, K. S., Nemeroff, C. B., Prange, A. J. (1984) Prevention of stress-induced gastric ulcers by dopamine agonists in the rat. Life Sci. 35: 2453–2458

Hjorth, S., Carlsson, A., Wikstrom, H., Lindberg, P., Sanchez, D., Hacksell, U., Arvidsson, L. E., Svensson, U., Nilsson, J. L. G. (1981) 3-PPP, a new entrally acting DA-receptor agonist with selectivity for auto-receptors. Ibid. 28: 1225–1238

Hjorth, S., Clark, D., Svensson, K., Carlsson, A., Thorberg, O. (1985) Subchronic administration of (-)-3-PPP and central dopamine receptor sensitivity changes. J. Neural Transmission 64: 187–198

Hong, J. S., Yoshikama, K., Kanamatsu, T., Sabol, S. L. (1985) Modulation of striatal enkephalinergic neurons by antipsychotic drugs. Federation Proc. 44: 2535–2539

Hornykiewicz, O. (1982) Brain catecholamines in schizophrenia. A good case for noradrenaline. Nature 229: 484–486

Hsu, W. H., Schaffer, D. D., Dyer, D. C. (1986) The emetic effect of B-HT 920 and apomorphine in the dog: antagonism by haloperidol. Life Sci. 39: 1021–1026

Kobinger, W., Pichler, L. (1981) α_1 and α_2-adrenoceptor subtypes: Selectivity of various agonists and relative distribution of receptors as determined in rats. Eur. J. Pharmacol. 73: 313–321

Kohli, J. D., Glock, D., Goldberg, L. I. (1983) Selective DA_2 versus DA_1 antagonists activity of domperidone in the periphery. Ibid. 89: 137–141

Kosterlitz, H. W., Lydon, R. J., Watt, A. J. (1970) The effects of adrenaline, noradrenaline and isoprenaline on the inhibitory α-and β-adrenoceptors in the longitudinal muscle of the guinea-pig ileum. Br. J. Pharmacol. 39: 398–413

Kusunoki, M., Taniyama, K., Tanaka, C. (1985) Dopamine regulation of ^3H acetylcholine release from guinea-pig stomach. J. Pharmacol. Exp. Ther. 234: 713–719

Laduron, P. M., Leysen, J. E. (1979) Domperidone, a specific in vitro dopamine antagonist, devoid of in vivo central dopaminergic activity. Biochem. Pharmacol. 28: 2161–2165

Li, S., Sivam, S. P., Hong, J.-S. (1986) Regulation of the concentration of dynorphin A_{1-8} in the striatonigral pathway by the dopaminergic system. Brain Res. 398: 390–392

Milanes, M. V., Vargas, M. L., Puig, M. M. (1984) Haloperidol treatment increases the biosynthesis and release of endorphins in guinea-pig ileum. J. Pharm. Pharmacol. 36: 446–449

Milanes, M. V., Vargas, M. L., Martinez, J. A., Perez, D., Brugger, A. J. (1985) Effects of chronic treatment with atypical neuroleptics on the biosynthesis and release of opioid peptides in guinea-pig ileum. Regul. Peptides 10: 319–327

Orloff, L. A., Orloff, M. S., Bunnett, N. W., Walsh, J. H. (1985) Dopamine and norepinephrine in the alimentary tract changes after chemical sympathectomy and surgical vagotomy. Life Sci. 36: 1625–1631

Palmer, M. R., Seiger, A., Hoffer, B. J., Olson, L. (1983) Modulatory interactions between enkephalin and catecholamines: Anatomical and physiological substrates. Fed. Proc. 42: 2934–2945

Puig, M. M., Gascon, P., Craviso, G. L., Musacchio, J. M. (1977) Endogenous opiate receptor ligand electrically induced release in the guinea-pig ileum. Science 195: 419–420

Quirion, R., Gaudreau, P., Martel, J. -C., St-Pierre, S., Zamir, N. (1985) Possible interactions between dynorphin and dopaminergic systems in rat basal ganglia and substantia nigra. Brain Res. 331: 358–362

Richelson, E., Nelson, A. (1984) Antagonism by neuroleptics of neurotransmitter receptors of normal human brain in vitro. Eur. J. Pharmacol. 103: 197–204

Sabol, S. L., Yoshikawa, K., Hong, J.-S. (1983) Regulation of methionine-enkephalin precursor messenger RNA in rat striatum by haloperidol and lithium. Biochem. Biophys. Res. Commun. 113: 391–399

Schuurkes, J. A. J., van Nueten, J. M. (1984) Domperidone improves myogenically transmitted antroduodenal coordination by blocking dopaminergic receptor sites. Scand. J. Gastroenterol. 19: 101–110

Skirboll, L. R., Grace, A. A., Bunney, B. S. (1979) Dopamine auto- and postsynaptic receptors: Electrophysiological evidence for differential sensitivity to dopamine agonist. Science 206: 80–82

Thal, L. J., Sharpless, N. S., Hirschhorn, I. D., Horowitz, S. G., Makman, M. H. (1983) Striatal met-enkephalin concentration increases following nigrostriatal denervation. Biochem. Pharmacol. 32: 3297–3301

van Meel, J. C. A., de Jonge, A., Timmersmans, P. B. M. W. M., van Zwieten, P. A. (1981) Selectivity of some alpha adrenoceptor agonists for peripheral alpha-1 and alpha-2 adrenoceptors in the normotensive rat. J. Pharmacol. Exp. Ther. 219: 760–767

van Nueten, J. M., Schuurkes, J. A. J. (1984) Studies on the role of dopamine and dopamine blockers in gastro-duodenal motility. Scand. J. Gastroenterol. 19: 89–99

Vargas, M. L., Martinez, J. A., Milanes, M. V. (1986) Pharmacological evidence for the existence of interactions between dopaminergic and opioid peptidergic systems in guinea-pig ileum myenteric plexus. Eur. J. Pharmacol. 128: 259–263

Vargas, M. L., Martinez, J. A., Milanes, M. V. (1987) Effects of droperidol on the biosynthesis and release of endogenous opioid peptides in guinea-pig ileum. Gen. Pharmacol. 18: 283–286

Vincent, S. R., Dalsgaard, C. -J., Schultzberg, M., Hokfelt, T., Christenson, I., Terenius, L. (1984) Dynorphin-immunoreactive neurons in the autonomic nervous system. Neuroscience 11: 973–988