Neuropharmacology Vol. 23, No. 12B, pp. 1473–1486, 1984
Printed in Great Britain.

0028-3908/84 $3.00 + 0.00

NEURONAL 5-HT RECEPTORS IN THE PERIPHERY

J. R. FOZARD
Merrell-Dow Research Institute, Strasbourg Center, 16, rue d'Ankara, 67084 Strasbourg, France

Summary—5-Hydroxytryptamine (5-HT) induces responses in neurones from all branches of the mammalian peripheral nervous system. Responses may be excitatory or inhibitory and are mediated through at least four distinct receptor sites.

One receptor mediates excitation in motoneurones and preganglionic sympathetic neurones and can be designated a D (or possibly 5-HT_2) receptor since "classical" antagonists such as methysergide, metergoline or cinanserin are potent and selective antagonists at this site. A second receptor mediating neuronal excitation can be positively identified on the basis of susceptibility to blockade by small concentrations of 1α H,3α,5α H-tropan-3-yl-3,5-dichlorobenzoate (MDL 72222) and the weak or negligible affinity, relative to 5-HT, of certain agonists such as 5-methoxytryptamine. Such sites mediate depolarization of sympathetic and parasympathetic neurones and excitation of both the cell bodies and terminals of primary afferent fibres. A third receptor, mediating neuronal excitation, is the classical M-receptor of Gaddum and Picarelli, at this stage clearly identified only on postganglionic parasympathetic neurones of the guinea-pig myenteric plexus. These sites can be differentiated from other excitatory 5-HT receptors since MDL 72222 is neither potent nor selective as an antagonist and 5-methoxytryptamine approaches the potency of 5-HT as an agonist. (3α-Homotropanyl)-1-methyl-5-fluoro-indole-3-carboxylic acid is a potent, surmountable antagonist of 5-HT at the M-receptor of the ileum, but is non-selective.

Neuronal inhibitory responses have been observed using electrophysiological techniques or by monitoring the decrease in depolarization-evoked release of transmitter in enteric, parasympathetic and sympathetic neurones. Largely negative results, using selective agonists and antagonists, allow the receptor(s) mediating inhibition to be clearly differentiated from the three neuronal excitatory receptors for 5-HT. Comparison of relative potencies of agonists suggests similarities with the 5-HT_1 recognition site of the central nervous system; no selective antagonist has yet emerged to permit their positive identification.

Key words: 5-HT receptors, neuronal excitation, neuronal inhibition.

1. INTRODUCTION AND SCOPE

5-Hydroxytryptamine (5-HT) induces responses in neurones from all branches of the mammalian peripheral nervous system, including preganglionic and postganglionic parasympathetic and sympathetic neurones, primary afferent cell bodies, axons and terminals, neurones of the enteric nervous system and motoneurones. Responses may be excitatory (depolarization/induction of firing/facilitation of synaptic transmission; increased transmitter release) or inhibitory (hyperpolarization/inhibition of firing/inhibition of synaptic transmission; decreased transmitter release) and in the majority of instances the available evidence implicates mediation through distinct 5-HT receptor sites. The primary objective of this review is to describe these sites in detail.

Several basic considerations have shaped the form and content of the presentation. First, and responding to the spirit of the title, where the principal evidence for a receptor of a peripherally extending neurone has been obtained largely from studies within the central nervous system (i.e. motoneurones; preganglionic sympathetic neurones), this has been discussed relatively briefly. Second, particular emphasis has been laid on the *functional* rather than the *electrophysiological* aspects of neuronal 5-HT receptor activation. This is a reflection not only of the bias of my personal interest and expertise, but also an acknowledgement of the several recent reviews in which the electrophysiological aspects of neuronal 5-HT receptor stimulation have been particularly well covered (Wallis, 1979; Gerschenfeld, Paupardin-Tritsch and Deterre, 1981; Gershon, 1981; Weight and Swenberg, 1981; Wallis, 1981; North, 1982). Finally, and for obvious reasons, particular emphasis has been placed on those studies in which the effects of selective agonists and antagonists have been explored; only with the aid of such data can the characteristics of individual neuronal 5-HT receptors be described.

2. HISTORICAL PERSPECTIVES

The very earliest pharmacological experiments carried out with 5-HT indicated clearly its capacity to interact with a variety of peripheral neurones. For instance, pain was reported following application of 5-HT to the blister base (Armstrong, Dry, Keele and Markham, 1953) and the cardiovascular responses to

5-HT in a number of species had important reflex components (reviewed by Page, 1958). But it was experiments carried out with perhaps the commonest of all pharmacological tissues, the guinea-pig ileum, which led to the first clear demonstration of a distinct neuronal receptor for 5-HT. Working essentially in parallel, the groups of Rocha e Silva and Gaddum, showed 5-HT to contract the ileum by two mechanisms, one of which involved excitation of the intramural cholinergic nerves (Rocha e Silva, Valle and Picarelli, 1953; Gaddum and Hameed, 1954). These efforts culminated in the seminal paper, co-authored by a representative from each of these groups, in which the first classification of 5-HT receptors in the periphery was described (Gaddum and Picarelli, 1957).

I cannot resist a brief comment on this rather maligned paper. Almost from the moment of its appearance, the classification of Gaddum and Picarelli was criticized largely on the basis of the use of morphine and dibenzyline, the drugs giving rise to the nomenclature, M and D (see, for example, Lewis, 1960; Brownlee and Johnson, 1963; Day and Vane, 1963; Drakontides and Gershon, 1968; Wurzel, 1966; Eyre, 1975; Wallis, 1981; Humphrey, 1983). Yet, after almost 30 years the basic concept that the guinea-pig ileum contains at least two distinct 5-HT receptors, one on the smooth muscle cells (the D-receptor) and a second associated with the intramural cholinergic nerves (the M-receptor), remains entirely valid. Of course, with hindsight, morphine and dibenzyline were clearly inappropriate tools for receptor classification. But there has been a tendency to overlook the fact that Gaddum and Picarelli substantiated their results with dibenzyline using lysergide, dihydroergotamine and bromolysergide. Moreover, in addition to morphine, they used cocaine which subsequently has been shown to be a selective and surmountable antagonist of the indirect cholinergic response to 5-HT in the guinea-pig ileum (Fozard, Mobarok Ali and Newgrosh, 1979). It bears emphasis that Gaddum and Picarelli themselves were under no illusion as to the deficiencies in the use of morphine. In the final sentence of their paper they acknowledge that, "there is ... no proof that ... [5-HT and morphine] ... act on the same receptors as one another". Given the essential correctness of the M and D receptor concept, its historical significance and its general understanding by the majority of pharmacologists, I believe it would be a mistake to abandon it. Rather, we should be seeking to modify, extend and, if necessary, redefine this terminology to incorporate new discovery. The M and D receptor terminology will be used in the course of this review. Reference will also be made to the $5\text{-HT}_1/5\text{-HT}_2$ receptor classification introduced on the basis of radioligand binding studies by Peroutka and Snyder (1979) and rapidly becoming accepted as a basis for the classification of both central and peripheral 5-HT receptors (Leysen, 1984).

3. 5-HYDROXYTRYPTAMINE RESPONSES OF THE MOTOR NERVOUS SYSTEM

The motoneurone is one example where pertinent studies into the effects of 5-HT have been carried out primarily on tissues within the brain or spinal cord. The predominant effect of 5-HT, applied iontophoretically to such neurones, is excitation although in some instances, hyperpolarization and decreased excitability have been described.

3.1. Excitation

The responses of neurones in the facial motor nucleus of the rat brain stem have been extensively studied by Aghajanian and his colleagues. Initial experiments using extracellular single unit recording revealed that the microiontophoretic administration of small amounts of 5-HT caused facilitation of excitatory synaptic inputs (McCall and Aghajanian, 1979). Subsequent intracellular recordings showed that 5-HT evoked a slow depolarization of the membrane, associated with an increase in input resistance probably by decreasing the resting membrane conductance to potassium ions (VanderMaelen and Aghajanian, 1980, 1982a). These responses can be mimicked by systemic administration of 5-methoxy-*N*,*N*-dimethyltryptamine, a 5-HT agonist which passes the blood–brain barrier (VanderMaelen and Aghajanian, 1982b). Broadly similar results have been obtained from spinal motoneurones where 5-HT has been shown to cause depolarization (Parry and Roberts, 1980) and facilitation of excitatory inputs in both rats (Barasi and Roberts, 1974; Parry and Roberts, 1980; White and Neumann, 1980, 1983) and cats (White and Neumann, 1980).

A number of selective 5-HT receptor antagonists has been used to explore the receptor type involved in 5-HT-evoked motoneurone excitation. Responses in both the facial nucleus and the spinal cord were blocked selectively by systemically- and/or iontophoretically-applied methysergide (Barasi and Roberts, 1974; McCall and Aghajanian, 1979; VanderMaelen and Aghajanian, 1980; White and Neumann, 1983), metergoline (McCall and Aghajanian, 1980; White and Neumann, 1983) cyproheptadine and cinanserin (McCall and Aghajanian, 1980). Following systemic administration, the doses of these antagonists required were generally small (McCall and Aghajanian, 1980) and comfortably within the range of those producing selective blockade of the D (5-HT_2) receptor for 5-HT (see, for example, Fozard, 1975; Fozard, 1982; Kalkman, Harms, Van Gelderin, Batink, Timmermans and Van Zwieten, 1983). It is safe to assume that D (5-HT_2) receptors mediate the excitatory response of the motoneurone to 5-HT.

3.2. Inhibition

There have been reports of transient hyperpolarization and decreased excitability of spinal motoneurones in response to 5-HT (Phillis, Tebecis and

York, 1968; Engberg, Flatman and Kadzielawa, 1976; White and Neumann, 1980, 1983). In the experiments of White and Neumann, inhibition did not outlast the period of application of current. Moreover, similar brief inhibitory responses have been recorded after electrophoretic application of a number of agents, including adrenoceptor antagonists, local anaesthetics and calcium and hydrogen ions (Engberg *et al.*, 1976; White and Neumann, 1983) suggesting that the inhibitory effect of 5-HT might be non-specific. Inhibition was resistant to blockade by methysergide and metergoline (White and Neumann, 1983); no evidence exists to indicate that the response is receptor-mediated.

4. 5-HYDROXYTRYPTAMINE RESPONSES OF THE SYMPATHETIC NERVOUS SYSTEM

4.1. Preganglionic neurone

The approach to recording responses of the sympathetic preganglionic neurones has been electrophysiological and in general involved the recording of activity in the preganglionic neurones in the intermediolateral cell column of the thoraco-lumbar cord. In studies employing microiontophoretic techniques, 5-HT has been found to excite the majority of neurones tested, although a significant minority were inhibited. Evidence that 5-HT excites and inhibits the sympathetic preganglionic neurone has also been obtained from experiments using isolated ganglia.

4.1.1. Excitation. That iontophoretically-applied 5-HT normally excites thoracic sympathetic preganglionic neurones has been well documented (De Groat and Ryall, 1967; Coote, Mcleod, Fleetwood-Walker and Gilbey, 1981; Kadzielawa, 1983; McCall, 1983). Excitation can be seen irrespective of whether the neurones are quiescent, spontaneously active or induced to discharge with excitatory amino acids such as L-glutamate and DL-homocysteic acid. Distinct receptors appear to mediate the excitatory response to 5-HT, since iontophoretic and/or systemic administration of methysergide, metergoline or cinanserin attenuated the response to 5-HT, without affecting the responses to the excitatory amino acids (Kadzielawa, 1983; McCall, 1983). For methysergide and metergoline, given systemically, the doses used were within the range of those which selectively inhibit responses to 5-HT, mediated through D(5-HT_2) receptors (Fozard, 1975; Fozard, 1982; Kalkman *et al.*, 1983), implicating these sites as mediators of the excitatory response to 5-HT in preganglionic sympathetic neurones. Excitatory 5-HT receptors are almost centainly present on the sympathetic preganglionic nerve terminals within rabbit superior cervical ganglion (Wallis and Woodward, 1975; Wallis, Williams and Wali, 1978); their pharmacological characteristics have not been determined.

4.1.2. Inhibition. 5-Hydroxytryptamine inhibited firing in 14% of the thoracic preganglionic neurones tested both by Coote *et al.* (1981) and Kadzielawa (1983). Inhibition was usually limited only to the period of ejection, after which firing increased rapidly to reach or even exceed the previous control level. Coote *et al.* (1981) concluded that neuronal inhibition was most likely due to an action of the creatinine which was ejected along with 5-HT since the response was never observed when the bimaleate salt was used. However, Kadzielawa (1983) obtained inhibition in precisely the same proportion of his cells, using the hydrochloride salt of 5-HT. There is no strong evidence that the inhibitory response evoked by 5-HT in thoracic sympathetic preganglionic neurones is receptor-mediated.

In contrast, careful experiments, carried out with a number of sympathetic ganglia, have revealed inhibitory effects of 5-HT on the preganglionic neuronal terminals. In the cat superior cervical ganglion, for instance, 5-HT inhibited ganglionic transmission at concentrations which had minimal and inconsistent effects on the ganglionic surface potential (De Groat and Lalley, 1973; Haefely, 1974) and no effect on depolarization induced directly by the nicotine receptor antagonist, dimethylphenylpiperazinium iodide (DMPP) (Haefely, 1974). Dun and Karczmar (1981) essentially confirmed these observations for the rabbit superior cervical ganglion. No antagonist of the presynaptic inhibitory action of 5-HT has yet emerged despite a number of compounds having been explored in this respect. The response was resistant to blockade by lysergide, methysergide, morphine, atropine, phenoxybenzamine, dihydroergotamine and picrotoxin; at doses up to those which themselves caused inhibition, methiothepin was also ineffective (De Groat and Lalley, 1973; Haefely, 1974; Dun and Karczmar, 1981). A role for D (5-HT_2) receptors, muscarinic cholinoceptors or α_1-adrenoceptors is, therefore, unlikely. In the experiments of Haefely (1974) both lysergide and methysergide *mimicked* 5-HT in inhibiting ganglion transmission. These compounds may, therefore, have *agonist* activity at the inhibitory 5-HT receptor of the preganglionic sympathetic neurone as they appear to have at neuronal inhibitory 5-HT receptors elsewhere (see Sections 4.2.2 and 7.2 below). In general, however, the putative 5-HT receptor, mediating 5-HT inhibition of preganglionic sympathetic neurones, remains at this stage undefined.

4.2. Postganglionic neurone

Electrophysiological and/or transmitter release experiments have clearly demonstrated both excitatory and inhibitory effects of 5-HT on the cell bodies, axons or terminals of sympathetic postganglionic neurones.

4.2.1. Excitation. An excitatory effect of 5-HT on sympathetic ganglion cells manifested as rapid depolarization, induction of firing in postganglionic nerves or facilitation of transmission, has been frequently observed (see reviews by Trendelenburg, 1967; Hac-

fely, 1972; Wallis, 1979, 1981; Weight and Swenburg, 1981). 5-Hydroxytryptamine also depolarizes sympathetic postganglionic axons (Nash and Wallis, 1981) and excites certain axon terminals, resulting in the release of noradrenaline (Jacob and Poite-Bevierre, 1960; Fozard and Mwaluko, 1976; Göthert and Dührsen, 1979). The fast depolarization of the ganglion cells is accompanied by a fall in membrane resistance (Wallis and North, 1978) and is generated by increases in Na^+ and K^+ conductance (Wallis and Woodward, 1975; Wallis and North, 1978). Occasionally, a slow, late depolarization of sympathetic ganglion cells has been observed in response to 5-HT (De Groat and Lalley, 1973; Haefely, 1974; Kiraly, Ma and Dun, 1983). In the guinea-pig coeliac ganglion, such responses were accompanied by an *increase* in membrane resistance (Kiraly *et al.*, 1983) and thus differed fundamentally from the fast depolarizing responses described and evaluated pharmacologically by most investigators.

There can be little doubt that excitation of sympathetic postganglionic neurones by 5-HT is mediated by distinct 5-HT receptors. For instance, excitatory responses are not affected by nicotine, muscarine or histamine receptor antagonists (see Trendelenburg, 1967; Fozard and Mobarok Ali, 1978a; Wallis, 1979). Moreover, tachyphylaxis to 5-HT occurs readily and is not crossed to other postganglionic neuronal excitatory stimuli (Haefely, 1974; Fozard and Mobarok Ali, 1978a; Wallis and North, 1978). Both agonists and putative antagonists have been used in attempts to characterize the 5-HT receptor mediating excitation of the sympathetic postganglionic neurone.

Several compounds structurally related to 5-HT have been found to have qualitatively similar excitatory activity to 5-HT on the inferior mesenteric (Gyermek and Bindler, 1962a) and superior cervical (Haefely, 1974) ganglia of the cat, the superior cervical ganglion of the rabbit (Wallis and Nash, 1981) and the sympathetic nerve terminals of the rabbit heart (Fozard and Mobarok Ali, 1978a; Göthert and Dührsen, 1979). In those cases where responses were definitely established to be 5-HT receptor mediated, the agreement between relative potencies as stimulants at the ganglion and at the terminal fibres was generally good. For instance, a number of hydroxylated tryptamine analogues, including those methylated at the terminal N atom, were consistently close to 5-HT in activity at each site. Tryptamine was a weak stimulant, both of the ganglion cells and the cardiac sympathetic nerves. However, perhaps the most striking feature of these studies was the fact that 5-methoxytryptamine, which is an active stimulant at a variety of 5-HT receptors, including those on enteric cholinergic neurones (see detailed discussion in Fozard and Mobarok Ali, 1978a) was devoid of agonist activity at either the ganglion (Gyermek and Bindler, 1962a; Wallis and Nash, 1981) or the terminal (Fozard and Mobarok Ali, 1978a) excitatory 5-HT receptor. It would be unwise to draw detailed conclusions from these agonist studies. Nevertheless, the data point to substantial similarities between the receptors of the cell body and the terminals of the sympathetic postganglionic neurone and provide the basis of comparison with other 5-HT receptor sites (see Sections 6.1 and 7.1 below).

Until recently, the search for selective "silent" antagonists of the excitatory effect of 5-HT had met with little success. Classical 5-HT receptor antagonists, such as lysergide and methysergide, were not effective (Gyermek and Bindler, 1962b; De Groat and Lalley, 1973; Haefely, 1974; Fozard and Mobarok Ali, 1978a) as indeed was morphine (Haefely, 1974; Fozard and Mobarok Ali, 1978a; Lansdown, Nash, Preston, Wallis and Williams, 1980). Picrotoxin was identified by De Groat and Lalley (1973) as an antagonist of 5-HT depolarization of the cat superior cervical ganglion; blockade was, however, not selective since excitatory responses to GABA were inhibited at similar concentrations. Quipazine has been shown to block selectively depolarization evoked by 5-HT in both rabbit and rat superior cervical ganglia (Lansdown *et al.*, 1980; Ireland, Straughan and Tyers, 1982). Blockade was slow in onset, poorly surmountable and not reversed by washing (Lansdown *et al.*, 1980). Moreover, at the concentrations used, quipazine has stimulant and/or blocking activity at a variety of other 5-HT receptors (Hong and Pardo, 1966; Lansdown *et al.*, 1980; Göthert, 1982), clearly limiting its use as a tool to discriminate between these sites. Amongst other agents which have been shown to inhibit selectively excitatory responses to 5-HT in postganglionic sympathetic neurones, are (−)-propranolol (Weinstock and Schechter, 1975), metoclopramide (Fozard and Mobarok Ali, 1978b; Wallis and Nash, 1980; Ireland *et al.*, 1982; Ireland, Fortune and Tyers, 1983) and cocaine (Gyermek and Bindler,1962b; De Groat and Lalley, 1973; Fozard *et al.*, 1979), and a number of its analogues (Fozard, 1979; Fozard *et al.*, 1979, Fozard, 1983a). All of these agents have the obvious drawback that they display other pharmacological actions at similar or smaller concentrations to those effective against 5-HT.

Recently, a series of substituted benzoic acid esters of tropine was synthesised (Fozard and Gittos, 1983), several of which proved to be both potent and highly selective antagonists at the 5-HT receptor mediating excitation of sympathetic postganglionic neurones. The most active compound, (1α H,3α,5α H-tropan-3-yl-3,5-dichlorobenzoate; MDL 72222) blocked, at nanomolar concentrations, release of noradrenaline evoked from the rabbit heart by activation of the excitatory 5-HT receptors present on the sympathetic terminal fibres (Fozard, 1984). Blockade was selective since 1000-fold greater concentrations were required to inhibit responses to the nicotine receptor agonist, DMPP (Fozard, 1984). The drug MDL 72222 was similarly a selective, surmountable antagonist of fast depolarization re-

sponses induced by 5-HT in cells of both rat (Fortune and Ireland, 1984) and rabbit (Wallis D. I., personal communication) superior cervical ganglion, although for both these tissues somewhat larger concentrations were required for blockade than were necessary on the heart.

At the present time, the receptor for 5-HT mediating excitation of postganglionic sympathetic neurones can best be characterized by susceptibility to blockade by MDL 72222 and by metoclopramide. The clear lack of agonist activity of 5-methoxytryptamine is remarkable in view of the powerful effects of this compound at other 5-HT receptors, including the M-receptor of the guinea-pig ileum; this also provides a means by which these sites can be distinguished.

4.2.2. Inhibition. As discussed above, the depression of ganglionic transmission, seen with small amounts of 5-HT, almost certainly reflects primarily a presynaptic inhibitory effect of 5-HT (Haefely, 1974; Dun and Karczmar, 1981). The prominent after-hyperpolarization of cells from rabbit superior cervical ganglion, which succeeds the depolarization, and which is seen prominently in sucrose-gap recordings, is similar to that seen following depolarization with nicotine receptor agonists and appears to be due to the activity of an electrogenic sodium pump (Wallis and Woodward, 1975; Nash and Wallis, 1981). On the other hand, both De Groat and Lalley (1973) and Haefely (1974) have documented postsynaptic hyperpolarizing responses in cat superior cervical ganglion. However, no detailed analysis of these responses was made and therefore electrophysiological experiments in the ganglion provide no convincing evidence for a postsynaptic inhibitory response to 5-HT, mediated through distinct 5-HT receptors. In contrast, there is good evidence from functional studies that the *terminals* of certain postganglionic sympathetic neurones are endowed with 5-HT receptors which result in inhibition of depolarization-induced, transmitter release when activated.

McGrath and Shepherd were the first to demonstrate unequivocally an inhibitory effect of 5-HT on release of transmitter from postganglionic sympathetic neurones (McGrath and Shepherd, 1976; McGrath, 1977; McGrath and Shepherd, 1978). They used strips of dog saphenous vein, whose sympathetic neuronal transmitter stores had been labelled with [^{3}H]noradrenaline, and demonstrated inhibition of both ^{3}H-overflow and the contractile response in response to electrical stimulation of the sympathetic nerves or depolarization with potassium. This basic observation was confirmed for the dog saphenous vein by Feniuk and his colleagues (Feniuk, Humphrey and Watts, 1979; Watts, Feniuk and Humphrey, 1981) and by Müller-Schweinitzer (1981). Evidence suggestive of prejunctional inhibitory responses to 5-HT has also been obtained in rabbit basilar artery (Bevan, Duckles and Lee, 1975), dog tibial artery (McGrath 1977), rat mesenteric vasculature (Kubo and Su, 1983) and guinea-pig atria (Adler-Graschinsky, 1983) *in vitro* and using cardiac and/or femoral vascular responses to sympathetic nerve stimulation in anaesthetized dogs (Martinez and Lokhandwala, 1980; Feniuk, Humphrey and Watts, 1981a; Kimura and Satoh, 1983), and cats (Humphrey, Fenuik and Watts, 1983). On the other hand, prejunctional inhibitory 5-HT receptors appear to be absent from the sympathetic nerves of the rabbit heart (Fozard and Muscholl, 1977) and pulmonary arteries from both rabbit (Endo, Starke, Bangerter and Taube, 1977) and man (Freeman, Rorie and Tyce, 1981).

The majority of attempts to characterize the inhibitory 5-HT receptor has been carried out with the dog saphenous vein. Although no selective antagonist of these sites has yet been described, the use of a large number of compounds, with known pharmacological selectivities, allows all reasonable alternative explanations to be eliminated. For instance, the response was not blocked by phentolamine, yohimbine, propranolol, haloperidol, cyproheptadine, ketanserin, morphine, metoclopramide, cocaine, atropine, mepyramine, cimetidine or metiamide (McGrath, 1977; Feniuk *et al.*, 1979; Feniuk, Humphrey and Watts, 1981b; Engel, Göthert, Müller-Schweinitzer, Schlicker, Sistonen and Stadler, 1983; Humphrey *et al.*, 1983). Methysergide appears to be partial agonists at this site, inhibiting responses to 5-HT only at concentrations which themselves cause inhibition (Feniuk *et al.*, 1979; Watts *et al.*, 1981). Neither in domethacin nor meclofenate were effective antagonists of 5-HT (McGrath, 1977; Feniuk *et al.*, 1979), hence ruling out a role for the products of cyclooxygenase in the response. The prejunctional inhibitory 5-HT receptors in tissues other than the dog saphenous vein have been less rigorously studied; experiments with methysergide and cyproheptadine in the anaesthetized dog suggest that the presynaptic inhibitory response to 5-HT is not mediated by D (5-HT$_2$) receptors (Martinez and Lokhandwala, 1980; Feniuk *et al.*, 1981b; Kimura and Satoh, 1983).

Several authors have described the comparative effects of various structural analogues of 5-HT as stimulants at the inhibitory prejunctional 5-HT receptor of the dog saphenous vein. Several 5-carboxamide tryptamine derivatives were found to be potent inhibitors of transmitter release, but inactive or markedly weaker as agonists at the 5-HT$_2$ receptors of the rabbit aorta or the M receptors of the guinea-pig ileum (Feniuk *et al.*, 1981b; Humphrey *et al.*, 1983). The remarkable potency and selectivity of 5-carboxamide tryptamine for the prejunctional 5-HT receptor in the dog saphenous vein was confirmed by Engel *et al.* (1983) who also defined the relative potency of 11 other 5-HT analogues, and of 5-HT itself at this site. From linear regression correlation analysis, the site had clear similarities both to the [^{3}H]5-HT recognition site(s) and to the 5-HT

autoreceptor in the cortex of the rat brain (Engel *et al.*, 1983).

In conclusion, the absence of a selective antagonist for the inhibitory 5-HT receptor of the postganglionic sympathetic neurone precludes its definitive identification. At this stage, the receptor can best be identified by the high affinity shown by certain 5-carboxamide tryptamine analogues, the absence of effect of established 5-HT receptor antagonists plus the fact that methysergide is a partial agonist.

5. 5-HYDROXYTRYPTAMINE RECEPTORS OF THE PARASYMPATHETIC NERVOUS SYSTEM

A strong case has been made for considering the cholinergic nerves of the gut, which include both pre- and postganglionic parasympathetic neurones, as part of the enteric nervous system (Gershon, Dreyfus and Rothman, 1979; Furness and Costa, 1980; North, 1982) and this has been conceded in the present review. Although, inevitably, this has diminished the scope of this section, it should be emphasized that discussion of many of the effects of 5-HT on enteric neurones (see Section 7 below) would quite properly pertain to elements of the parasympathetic nervous system.

The work of Gyermek (1962), Vanov (1965) and Saum and De Groat (1973) has clearly documented the excitant effects of 5-HT on the parasympathetic innervation to the bladder of dog, rat and cat, respectively. Saum and De Groat (1973) further demonstrated marked inhibitory effects of 5-HT on transmission through the pelvic ganglion, although whether 5-HT was acting pre- or postsynaptically in this respect was not established. No clear definition of any of the putative 5-HT receptors involved in these responses is possible. In the cat, picrotoxin blocked the excitatory response to 5-HT although no evidence of selectivity was presented; inhibition was resistant to blockade both by α- and β-adrenoceptor antagonists and by methysergide but no antagonist was described (Saum and De Groat, 1973).

More recently, the excitatory effects of 5-HT on the parasympathetic neurones of rat bronchi (Aas, 1983) and rabbit heart (Fozard J. R., unpublished) have been described. In the rabbit heart, release of acetylcholine resulted from stimulation of the postganglionic neurones and specific 5-HT receptors appear to be involved since rapid and selective receptor desensitization can be achieved with an excess of 5-HT (Fozard J. R., unpublished). The indirect cholinergic response to 5-HT was inhibited by MDL 72222 at concentrations similar to those which blocked release of transmitter evoked by 5-HT from the sympathetic neurones (Fozard J. R., unpublished). Since the indirect cholinergic response to DMPP was unaffected by MDL 72222 (Fozard J. R., unpublished), the data are consistent with similar excitatory 5-HT receptors being present on the postganglionic fibres of each branch of the autonomic nervous system supplying the rabbit heart. This conclusion may be considered surprising in view of the lack of effect of MDL 72222 at the M-receptor, mediating the indirect cholinergic response to 5-HT on the guinea-pig ileum (Fozard, 1984; see Section 7.1 below); consistent with it, however, is the fact that 5-methoxytryptamine, which is a potent agonist at the M-receptor, is not an agonist at the excitatory 5-HT receptor of either the parasympathetic or the sympathetic neurones of the rabbit heart (Fozard and Mobarok Ali, 1978a; Fozard J. R., unpublished).

6. 5-HYDROXYTRYPTAMINE RESPONSES OF THE SENSORY NERVOUS SYSTEM

5-Hydroxytryptamine is primarily an excitant of the neurones of the sensory nervous system. Only in rare instances has inhibition been seen.

6.1. Excitation

5-Hydroxytryptamine has long been recognized as a potent excitant of afferent fibres in a wide variety of peripheral nerves. The effects are manifested as prominent reflex effects on respiration and within the cardiovascular system (see for example Douglas and Toh, 1953; Comroe, Van Lingen, Stroud and Roncoroni, 1953; Ginzel and Kottegoda, 1954; Jacobs and Comroe, 1971) and the generation of pain in man and animals (Armstrong *et al.*, 1953; Lindahl, 1961; Guzman, Braun and Lim, 1962; Sicuteri, Fanciullacci, Franchi and Del Bianco, 1965). Stimulation has been recorded directly from the terminals, axons and/or cell bodies of cutaneous (Fjällbrant and Iggo, 1961; Beck and Handwerker, 1974), skeletal muscle (Mense and Schmidt, 1974; Fock and Mense, 1976), and visceral (Douglas and Ritchie, 1957; Higashi, 1977; Neto, 1978; Higashi, Ueda, Nishi, Gallagher and Shinnick-Gallagher, 1982; Wallis, Stansfeld and Nash, 1982) fibres. With rare exceptions it is the unmyelinated C fibres which respond to 5-HT (Fock and Mense, 1976; Higashi and Nishi, 1982; Higashi *et al.*, 1982; Stansfeld and Wallis, 1982).

A particularly detailed analysis of the excitant effects of 5-HT on afferent neurones has been made using visceral primary afferent neurones of cat, rabbit and rat. With extracellular recording techniques, Sampson and Jaffe (1975) and Simonds and De Groat (1980) showed depolarization and increased firing in cat vagal afferents. Using intracellular (Higashi, 1977; Higashi and Nishi, 1982; Higashi *et al.*, 1982) or sucrose gap (Wallis *et al.*, 1982; Stansfeld and Wallis, 1982) recording, 5-HT was found to induce rapid depolarization in the majority of the type C neurones of the rabbit nodose ganglion and a prominent after-hyperpolarization was observed. Neto (1978) and Ireland *et al.* (1982) recorded depolarizing responses to 5-HT from the isolated vagus nerves of rabbit and rat respectively. The

Bezold–Jarisch effect of 5-HT in the anaesthetized rat (Salmoiraghi, Page and McCubbin, 1956; Krayer, 1961; Paintal, 1973) affords a convenient *in vivo* measure of vagal afferent fibre stimulation (Fozard, 1982; Fozard and Host, 1982; Fozard, 1984). Attempts to define the receptor mediating the excitatory responses to 5-HT in sensory afferent fibres have been carried out using these techniques.

Depolarizing responses of afferent neurones to 5-HT were unaffected by atropine, hexamethonium, mecamylamine, methysergide or lysergide (Neto, 1978; Higashi and Nishi, 1982; Ireland *et al.*, 1982; Wallis *et al.*, 1982) hence ruling out an intermediary role for cholinoceptors or the D (5-HT_2) receptor. Picrotoxin was shown to be a surmountable antagonist of 5-HT-evoked excitation of cat vagal afferent fibres (Simonds and De Groat, 1980). Blockade was, however, only poorly selective. Moreover, picrotoxin is not a selective antagonist of excitatory responses to 5-HT in rabbit or rat vagal afferents (Higashi *et al.*, 1982; Ireland *et al.*, 1982; Wallis *et al.*, 1982). (+)-Tubocurarine, which blocks type A excitatory responses induced by 5-HT in molluscan neurones (Gerschenfeld *et al.*, 1981), inhibited 5-HT-induced depolarization of the cells of rabbit nodose ganglion (Higashi and Nishi, 1982). However, (+)-tubocurarine was non-selective in this respect, being a more potent antagonist of depolarizing responses to acetylcholine and GABA (Higashi *et al.*, 1982).

Several compounds have been claimed as selective antagonists of the excitatory response to 5-HT of vagal primary afferents. Quipazine, which blocks depolarization induced by 5-HT in rat and rabbit superior cervical ganglia (Lansdowne *et al.*, 1980; Ireland *et al.*, 1982), produces a similar, slowly-developing blockade of responses to 5-HT in rabbit nodose ganglion (Wallis *et al.*, 1982) and is a non-surmountable, though selective, antagonist of 5-HT on the rat vagus nerve (Ireland *et al.*, 1982). Metoclopramide is both an antagonist of 5-HT on rat vagus nerve (Ireland *et al.*, 1982) and of the Bezold–Jarisch component of the cardiovascular response to 5-HT in the anaesthetized rat (Fozard and Host, 1982; Donatsch, Engel, Richardson and Stadler, 1984a). Cocaine and a number of related compounds are similarly selective antagonists of the Bezold–Jarisch effect of 5-HT (Fozard and Host, 1982). As tools to distinguish responses mediated through neuronal 5-HT receptors, however, all these agents have the drawback that they manifest other pharmacological activities at doses or concentrations similar to those blocking effects of 5-HT. This particular criticism cannot be levelled at MDL 72222, which has been shown to be a selective antagonist of depolarizing responses evoked by 5-HT from rabbit nodose ganglion (Azami, Fozard, Round and Wallis, 1984), and rat and rabbit vagus nerve (Donatsch *et al.*, 1984a; Fortune and Ireland, 1984) and of the Bezold–Jarisch effect of 5-HT (Fozard, 1984) at doses and concentrations which are otherwise pharmacologically inert (Fozard, 1984). Several compounds, related structurally to MDL 72222, are similarly highly potent antagonists of vagal afferent neuronal depolarization caused by 5-HT and/or its Bezold–Jarisch effect (Fozard and Gittos, 1983; Donatsch *et al.*, 1984a; Donatsch, Engel, Richardson and Stadler, 1984b).

There have been relatively few studies dealing with agonist activity at excitatory 5-HT receptors on sensory afferent fibres. It is, however, important to note that in the rabbit nodose ganglion, loss of, or masking of, the hydroxyl group in position 5 of the indole nucleus (e.g. tryptamine of 5-methoxytryptamine) results in a greatly reduced stimulant effect (Wallis *et al.*, 1982). Consistent with this, 5-methoxytryptamine cannot evoke the Bezold–Jarisch effect in the anaesthetized rat (Fozard, 1983b). The lack of agonist activity of 5-methoxytryptamine at this site can be considered an important distinguishing feature since the compound is a potent agonist at 5-HT receptors elsewhere in the body (Vane, 1959; Fozard, 1983b) including the excitatory neuronal receptor of the enteric cholinergic neurones (Fozard and Mobarok Ali, 1978a; see Section 7.1. below).

In conclusion, the principal distinguishing features of the receptor for 5-HT, which mediates excitation of sensory afferent fibres, is its susceptibility to blockade by MDL 72222 and metoclopramide, and the fact that 5-methoxytryptamine is inactive as an agonist.

6.2. Inhibition

In general, less than 5% of visceral primary afferents respond to 5-HT with hyperpolarization (Higashi, 1977; Higashi and Nishi, 1982; Higashi *et al.*, 1982). The response has not been investigated in detail and no conclusions can be drawn as to the receptor type which might be involved.

7. 5-HYDROXYTRYPTAMINE RECEPTORS OF THE ENTERIC NERVOUS SYSTEM

Electrophysiological studies distinguish two main types of neurone within the enteric nervous system, i.e. type 1 (or S) cells respond to focal stimulation with a nicotinic fast excitatory postsynaptic potential, and in this respect are similar to other autonomic ganglion cells; type 2 (or AH) cells display no nicotinic excitatory postsynaptic potential, and the action potential is followed by a prolonged hyperpolarization (see Furness and Costa, 1980; North, 1982). Both type 1 (S) and type 2 (AH) cells are present in the myenteric plexus whereas the neurones of the submucous plexus seem to be exclusively of the type 1 (S) type (Furness and Costa, 1980). The type 1 (S) cells are likely to include the cholinergic neurones whose excitation results in the indirect cholinergic response to 5-HT in the ileum (Gaddum and Picarelli, 1957). Both electrophysiological and func-

tional studies clearly indicate that 5-HT can elicit excitation and inhibition of neurones from the enteric nervous system.

7.1. Excitation

Excitatory effects of 5-HT on neurones of the guinea-pig myenteric plexus have been shown directly using extracellular (Dingledine, Goldstein and Kendig, 1974; Sato, Takayanagi and Takagi, 1974) and intracellular (Wood and Mayer, 1978, 1979; Johnson, Katayama and North, 1980; North, Henderson, Katayama and Johnson, 1980; Johnson, Katayama, Morita and North, 1981) recording techniques. Whether administered by superfusion or iontophoresis, around 50% of the type 1 (S) cells failed to respond to 5-HT and of the remainder, 30–35% were depolarized (Johnson *et al.*, 1980, 1981). Depolarization was seen rather more often in type 1 (S) than in type 2 (AH) cells (Johnson *et al.*, 1980). 5-Hydroxytryptamine similarly depolarized neurones in the guinea-pig submucous plexus (Hirst and Silinsky, 1975; Neild, 1981). In direct contrast to the situation in sympathetic postganglionic and afferent neurones, depolarizing responses of the myenteric neurones to 5-HT were associated with an *increase* in membrane resistance, probably the result of inactivation of the membrane potassium conductance (Johnson *et al.*, 1980).

One functional consequence of the depolarization of guinea-pig enteric neurones is the release of acetylcholine (Adam-Vizi and Vizi, 1978; Kilbinger, Kruel, Pfeuffer-Friederich and Wessler, 1982), resulting in an indirect cholinergic contractile response (Rocha e Silva *et al.*, 1953; Sinha and West, 1953; Gaddum and Hameed, 1954; Gaddum and Picarelli, 1957; Brownlee and Johnson, 1963; Day and Vane, 1963; Fozard and Mobarok Ali, 1978a; Huidobro-Toro and Foree, 1980). The failure of a wide variety of receptor antagonists to block selectively the indirect cholinergic responses to 5-HT (see, for example, Brownlee and Johnson, 1963; Day and Vane, 1963), plus the evidence of rapid and selective receptor desensitization (Gaddum, 1953; Rocha e Silva *et al.*, 1953), have established beyond reasonable doubt that 5-HT activates specific receptors on the ileal cholinergic nerves, originally designated "M" by Gaddum and Picarelli (1957). An indirect cholinergic response to 5-HT can be elicited elsewhere in the guinea-pig gastrointestinal tract (Akubue, 1966; Yamaguchi, 1972; Kamikawa and Shimo, 1983) and in gut preparations from other species (see Garattini and Valzelli, 1965; Drakontides and Gershon, 1968; Burks, 1973).

Although the M-receptor can be rapidly and selectively desensitized by 5-HT receptor agonists (Gyermek, 1966; Fozard and Mobarok Ali, 1978a; Huidobro-Toro and Foree, 1980), including phenylbiguanide (Drakontides and Gershon, 1968), no satisfactory "silent" competitive antagonist has yet emerged to allow its positive identification. Metoclopramide, which is a surmountable antagonist at excitatory 5-HT receptors on postganglionic sympathetic and sensory afferent fibres (see Sections 4.2.1 and 6.1 above), is a *partial* agonist at the M-receptor of the ileum (Kilbinger *et al.*, 1982). Historically, it is of interest to recall that cocaine and a number of its analogues are both surmountable and, to some extent, selective antagonists of 5-HT on the ileum (Fozard *et al.*, 1979; Fozard, 1983a). A recent preliminary report claims (3α-homotropanyl)-1-methyl-5-fluoro-indole-3-carboxylic acid to be a competitive antagonist of 5-HT in the ileum with a pA_2 value of 9.0 (Donatsch *et al.*, 1984b). Although the compound is not selective for the ileum M-receptor, the finding raises hopes for the early development of molecules with improved selectivity at this site. It bears emphasis that MDL 72222 is *not* a selective antagonist at the M-receptor (Fozard, 1984), thus clearly differentiating this site from the excitatory receptor of certain postganglionic sympathetic and parasympathetic neurones and sensory afferent fibres (see Sections 4.2.1, 5 and 6.1 above).

The use of selective agonists has similarly allowed discrimination between the M-receptor of the ileum and neuronal excitatory 5-HT receptors elsewhere in the peripheral nervous system. As noted above, loss (or masking) of the hydroxyl group in the 5-position of several tryptamine analogues leads to a significant loss of activity relative to 5-HT as stimulants at certain postganglionic sympathetic and parasympathetic and visceral afferent neuronal 5-HT receptors; 5-methoxytryptamine, in particular, is inactive (Gyermek and Bindler, 1962a; Fozard and Mobarok Ali, 1978a; Wallis and Nash, 1981; Stansfeld and Wallis, 1982). By contrast, 5-methoxytryptamine is a powerful stimulant of the M-receptor of the ileum, with a potency in this respect close to that of 5-HT (Bertaccini and Zamboni, 1961; Fozard and Mobarok Ali, 1978a).

Inevitably, since no satisfactory discriminatory antagonist of the effects of 5-HT at the M-receptor has yet been described, no precise way of identifying responses mediated through such sites can be given. The receptor can perhaps best be described at present in the following terms: a site at which the effects of 5-HT are blocked surmountably by certain cocaine analogues and by (3α-homotropanyl)-1-methyl-5-fluoro-indole-3-carboxylic acid, at which 5-methoxytryptamine has substantial affinity as an agonist, where metoclopramide is a partial agonist and for which MDL 72222, a selective antagonist of responses mediated through excitatory 5-HT receptors elsewhere in the peripheral nervous system, has negligible affinity.

7.2. Inhibition

Sound electrophysiological and functional evidence of inhibitory responses to 5-HT in the enteric nervous system has been obtained. For instance, some 10% of type 1 (S) cells and some 50% of type

2 (AH) cells tested by Johnson *et al.* (1980) responded to 5-HT with hyperpolarization. The response, which was associated with a marked fall in membrane resistance and considered to be caused by activation of the potassium membrane conductance, has not been pharmacologically defined. Moreover, since the effect was absent in calcium-free solutions, release of an inhibitory neurotransmitter by 5-HT could be involved (Johnson *et al.*, 1980).

Rather more thoroughly investigated has been the effect of 5-HT to inhibit release of acetylcholine from neurones in the enteric nervous system. North *et al.* (1980) recorded intracellularly from type 1 (S) neurones of guinea-pig myenteric plexus and showed 5-HT to depress concentration-dependently and consistently the amplitude of the evoked nicotinic excitatory postsynaptic potential. 5-Hydroxytryptamine did not affect the depolarization resulting from iontophoretic application of acetylcholine, strongly implicating a presynaptic site of action to inhibit release of acetylcholine (North *et al.*, 1980). Cyproheptadine, an antagonist at D (5-HT_2) receptors was not a selective antagonist of this effect. Moreover, although evidence of blockade was obtained with relatively large concentrations of both methysergide and lysergide, these compounds themselves depressed the excitatory postsynaptic potential suggesting partial agonist activity at this site (North *et al.*, 1980). In this respect there is a close parallel with the effects of these compounds to inhibit transmitter release from both the pre- and postganglionic sympathetic neurones (see Sections 4.1.2 and 4.2.2 above).

A presynaptic inhibitory mechanism could explain the blockade by small concentrations of 5-HT, of contractions of guinea-pig ileum evoked by transmural electrical stimulation (Gintzler and Musacchio, 1974). Preliminary details of direct evidence that 5-HT can inhibit release of acetylcholine evoked by a depolarizing stimulus from myenteric neurones have recently appeared (Kilbinger and Pfeuffer-Friederich, 1982; Pfeuffer-Friederich and Kilbinger, 1983). These authors labelled the transmitter stores of the guinea-pig myenteric plexus with [^{3}H]choline and monitored the release of [^{3}H]acetylcholine, evoked by electrical field stimulation. 5-Hydroxytryptamine inhibited, in a concentration-dependent manner, the evoked outflow of [^{3}H]acetylcholine. Inhibition was blocked surmountably by methiothepin (pA_2 7.7) and by methysergide, although only in concentrations much greater than those selective for D (5-HT_2) receptors (Kilbinger and Pfeuffer-Friederich, 1982). Consistent with the findings of North *et al.* (1980), lysergide had agonist activity at the inhibitory 5-HT receptor of the ileum (Pfeuffer-Friederich and Kilbinger, 1983). However, it should be emphasized that the precise site of action of 5-HT in inhibiting release of [^{3}H]acetylcholine has not at this stage been established with certainty; clearly, with the methods used, transmitter could be released from both the pre- and postsynaptic cholinergic neurones.

As with the inhibitory receptors for 5-HT in other areas of the mammalian peripheral nervous system, those found in the enteric nervous system cannot be defined with precision at the present time. The lack of effect of classical 5-HT antagonists, and the agonist effects of methysergide and lysergide, provide a clear link with the inhibitory receptor on sympathetic postganglionic neurones and indirectly, therefore, with both the 5-HT_1 recognition site and the autoreceptor of the brain (Engel *et al.*, 1983; see Section 4.2.2 above). The finding that methiothepin is a potent, competitive antagonist of 5-HT inhibitory responses in the myenteric plexus lends substantial support to this supposition, since methiothepin is a consistently effective antagonist of 5-HT at the autoreceptor with appreciable affinity for 5-HT_1 recognition sites (Göthert, 1982; Engel *et al.*, 1983).

FINAL CONCLUSIONS

Table 1 draws together the principal characteristics of the peripheral neuronal 5-HT receptors discussed in this review. It will be immediately obvious that despite significant recent progress, many gaps remain in our understanding of these sites. Nevertheless, a number of conclusions can be justified in the interest of defining an interim classification which can be modified as advances dictate.

The receptors of the motoneurones and preganglionic sympathetic neurones, which mediate excitatory responses to 5-HT, can with confidence be labelled D (5-HT_2) receptors on the basis of the careful antagonist studies described in Sections 3.1 and 4.1.1. Of the four other neuronal excitatory responses (in postganglionic sympathetic and parasympathetic fibres and afferent and enteric neurones), it can be equally certain that none involves a D (5-HT_2) receptor. The most parsimonious approach distinguishes just two other excitatory receptor types, one subserving excitation of certain sympathetic and parasympathetic postganglionic neurones and afferent fibres; the other, the M-receptor of Gaddum and Picarelli (1957), mediating release of acetylcholine from the enteric cholinergic neurones. The drug MDL 72222 enables these two sites to be clearly distinguished as does a careful analysis of the effects of 5-methoxytryptamine and metoclopramide. The designation of these sites as M with a subscript indicating their anatomical location (*A*fferent; *P*arasympathetic; *S*ympathetic) is offered as a provisional means of identification. Clearly, if the above reasoning turns out to be correct then the M_A, M_P and M_S designation could eventually be abandoned in favour of M with a single suitable subscript (say M_B). For consistency, the Gaddum and Picarelli M receptor could, at that point, be renamed M_A.

When inhibitory responses of peripheral neurones are considered, there is little hard pharmacological

Table 1. Classification of 5-HT receptors on mammalian peripheral neurones

Nervous system	Motor	Sympathetic			Parasympathetic		Afferent		Enteric	
Receptor distribution	Cell bodies	Preganglionic		Postganglionic	Preganglionic	Postganglionic	Cell bodies: Axons: Terminals		Presynaptic	Postsynaptic
Response elicited	Excitation	Inhibition	Excitation	Inhibition	Excitation	Inhibition	Excitation		Inhibition	Excitation
Antagonists	Methysergide Metergoline Cyproheptadine Cinanserin	None	Methysergide Metergoline	None	Metoclopramide MDL 72222	None	MDL 72222	Metoclopramide MDL 72222	Methiothepin	(3α-Homotropanyl)-1-methyl-5-fluoro-indole-3-carboxylic acid ester
Partial agonists		Methysergide Lysergide		Methysergide					Methysergide Lysergide	Metoclopramide
Agonists				5-Carboxamide tryptamine						5-Methoxytryptamine
Designation	D (5-HT$_2$)	5-HT$_1$?	D (5-HT$_2$)	5-HT$_1$?	M_S	?	M_P	M_A	5-HT$_1$?	M

data upon which to base a classification. There is, however, no evidence that the inhibitory sites present in both branches of the autonomic nervous system and the enteric nervous system differ from each other; indeed, with respect to the partial agonist effects of lysergide and methysergide, they are clearly similar. As a working hypothesis, it can be suggested that only one type of inhibitory 5-HT receptor exists in the mammalian peripheral nervous system. Moreover, from the studies of Engel *et al.* (1983), this could be a functional correlate of the 5-HT$_1$ recognition site(s) and have similarities to the 5-HT autoreceptor of cortex of the rat brain. The availability of 5-carboxamide tryptamine represents an important advance in our means of identifying these sites; only the development of a selective antagonist(s) for the putative 5-HT$_1$ receptor will allow vigorous test of the hypothesis.

REFERENCES

Aas P. (1983) Serotonin induced release of acetylcholine from neurons in the bronchial smooth muscle of the rat. *Acta physiol. scand.* **117:** 477–480.

Adam-Vizi V. and Vizi E. S. (1978) Direct evidence of acetylcholine releasing effect of serotonin in the Auerbach plexus. *J. Neural Trans.* **42:** 127–138.

Adler-Graschinsky E. (1983) Dual presynaptic effects of 5-hydroxytryptamine on peripheral noradrenergic synapses. *J. Auton. Pharmac.* **3:** 303–315.

Akubue P. I. (1966) The site of action of drugs on the isolated taenia caeci from the guinea-pig. *Br. J. Pharmac.* **27:** 347–365.

Armstrong D., Dry R. M. L., Keele C. A. and Markham J. W. (1953) Observations on chemical excitants of cutaneous pain in man. *J. Physiol., Lond.* **120:** 326–351.

Azami J., Fozard J. R., Round A. A. and Wallis D. I. (1984) Selective blockade by MDL 72222 of the depolarizing action of 5-hydroxytryptamine on vagal primary afferents. *Br. J. Pharmac.* **51:** 129P.

Barasi S. and Roberts M. H. T. (1974) The modification of lumbar motoneurone excitability by stimulation of a putative 5-hydroxytryptamine pathway. *Br. J. Pharmac.* **52:** 339–348.

Beck P. W. and Handwerker H. O. (1974) Bradykinin and serotonin effects on various types of cutaneous nerve fibres. *Pflügers Arch. Eur. J. Physiol.* **347:** 209–222.

Bertaccini G. and Zamboni P. (1961) The relative potency of 5-hydroxytryptamine like substances. *Archs int. Pharmacodyn. Ther.* **133:** 138–156.

Bevan J. A., Duckles S. P. and Lee T. J. F. (1975) Histamine potentiation of nerve and drug-induced responses of a rabbit cerebral artery. *Circulation Res.* **36:** 647–653.

Brownlee G. and Johnson E. S. (1963) The site of the 5-hydroxytryptamine receptor on the intramural nervous plexus of the guinea-pig isolated ileum. *Br. J. Pharmac.* **21:** 306–322.

Burks T. F. (1973) Mediation by 5-hydroxytryptamine of morphine stimulant actions in dog intestine. *J. Pharmac. exp. Ther.* **185:** 530–539.

Comroe J. H. Jr, Van Lingen B., Stroud R. C. and Roncoroni A. (1953) Reflex and direct cardiopulmonary effects of 5-OH-tryptamine (serotonin). *Am. J. Physiol.* **173:** 379–389.

Coote J. H., Macleod V. H., Fleetwood-Walker S. and Gilbey M. P. (1981) The response of individual sympathetic preganglionic neurones to microelectrophoretically applied endogenous monoamines. *Brain Res.* **215:** 135–145.

Day M. and Vane J. R. (1963) An analysis of the direct and

indirect actions of drugs on the isolated guinea-pig ileum. *Br. J. Pharmac.* **20:** 150–170.

De Groat W. C. and Lalley P. M. (1973) Interaction between picrotoxin and 5-hydroxytryptamine in the superior cervical ganglion of the cat. *Br. J. Pharmac.* **48:** 233–244.

De Groat W. C. and Ryall R. W. (1967) An excitatory action of 5-hydroxytryptamine on sympathetic preganglionic neurones. *Expl Brain Res.* **3:** 299–305.

Dingledine R., Goldstein A. and Kendig J. (1974) Effects of narcotic opiates and serotonin on the electrical behavior of neurons in the guinea pig myenteric plexus. *Life Sci.* **14:** 2299–2309.

Donatsch P., Engel G., Richardson B. P. and Stadler P. (1984a) ICS 205-930: a highly selective and potent antagonist at peripheral neuronal 5-hydroxytryptamine (5-HT) receptors. *Br. J. Pharmac.* **81:** 34P.

Donatsch P., Engel G., Richardson B. P. and Stadler P. A. (1984b) Subtypes of neuronal 5-hydroxytryptamine (5-HT) receptors as identified by competitive antagonists. *Br. J. Pharmac.* **81:** 33P.

Douglas W. W. and Ritchie J. M. (1957) On excitation of non-medulated afferent fibres in the vagus and aortic nerves by pharmacological agents. *J. Physiol., Lond.* **138:** 31–43.

Douglas W. W. and Toh C. C. (1953) The respiratory stimulant action of 5-hydroxytryptamine (serotonin) in the dog. *J. Physiol., Lond.* **120:** 311–318.

Drakontides A. B. and Gershon M. D. (1968) 5-Hydroxytryptamine receptors in the mouse duodenum. *Br. J. Pharmac.* **33:** 480–492.

Dun N. J. and Karczmar A. G. (1981) Evidence for a presynaptic inhibitory action of 5-hydroxytryptamine in a mammalian sympathetic ganglion. *J. Pharmac. exp. Ther.* **217:** 714–718.

Endo T., Starke K., Bangerter A. and Taube H. D. (1977) Presynaptic receptor systems on the noradrenergic neurons of the rabbit pulmonary artery. *Naunyn-Schmiedebergs Arch. Pharmac.* **296:** 229–247.

Engberg I., Flatman J. A. and Kadzielawa K. (1976) Lack of specificity of motoneurone responses to microiontophoretically applied phenolic amines. *Acta physiol. scand.* **96:** 137–139.

Engel G., Göthert M., Müller-Schweinitzer E., Schlicker E., Sistonen L. and Stadler P. A. (1983) Evidence for common pharmacological properties of [^{3}H] 5-hydroxytryptamine binding sites, presynaptic 5-hydroxytryptamine autoreceptors in CNS and inhibitory presynaptic 5-hydroxytryptamine receptors on sympathetic nerves. *Naunyn-Schmiedebergs Arch. Pharmac.* **324:** 116–124.

Eyre P. (1975) Atypical tryptamine receptors in sheep pulmonary vein. *Br. J. Pharmac.* **55:** 329–333.

Feniuk W., Humphrey P. P. A. and Watts A. D. (1979) Presynaptic inhibitory action of 5-hydroxytryptamine in dog isolated saphenous vein. *Br. J. Pharmac.* **67:** 247–254.

Feniuk W., Humphrey P. P. A. and Watts A. D. (1981a) Modification of the vasomotor actions of methysergide in the femoral arterial bed of the anaesthetized dog by changes in the sympathetic nerve activity. *J. Auton. Pharmac.* **1:** 127–132.

Feniuk W., Humphrey P. P. A. and Watts A. D. (1981b) Further characterization of pre- and post-junctional receptors for 5-hydroxytryptamine in isolated vasculature. *Br. J. Pharmac.* **73:** 191P–192P.

Fjällbrant N. and Iggo A. (1961) The effect of histamine, 5-hydroxytryptamine and acetylcholine on cutaneous afferent fibres. *J. Physiol., Lond.* **156:** 578–590.

Fock S. and Mense S. (1976) Excitatory effects of 5-hydroxytryptamine, histamine and potassium ions on muscular group IV afferent units: a comparison with bradykinin. *Brain Res.* **105:** 459–469.

Fortune D. H. and Ireland S. J. (1984) Antagonism by MDL 72222 of 5-HT-induced depolarizations of the rat isolated vagus nerve and superior cervical ganglion. *Br. J. Pharmac.* **81:** 170P.

Fozard J. R. (1975) The animal pharmacology of drugs used in the treatment of migraine. *J. Pharm. Pharmac.* **27:** 297–321.

Fozard J. R. (1979) Blockade of receptors for 5-hydroxytryptamine on the sympathetic nerves of the rabbit heart. In: *Advances in the Biosciences* (Langer S. Z., Starke K. and Dubocovich M. L., Eds), pp. 327–332. Pergamon, Oxford.

Fozard J. R. (1982) Basic mechanisms of antimigraine drugs. In: *Advances in Neurology. Headache: Physiopathological and Clinical Concepts* (Critchley M., Friedman A. P., Gorini S. and Sicuteri F., Eds), Vol. 33, pp. 295–307. Raven Press, New York.

Fozard J. R. (1983a) Differences between receptors for 5-hydroxytryptamine on autonomic neurones revealed by nor-(−)-cocaine. *J. Auton. Pharmac.* **3:** 21–26.

Fozard J. R. (1983b) Failure of 5-methoxytryptamine to evoke the Bezold–Jarisch effect supports homology of excitatory 5-HT receptors on the vagal afferent and postganglionic sympathetic neurones. *Eur. J. Pharmac.* **95:** 331–332.

Fozard J. R. (1984) MDL 72222: a potent and highly selective antagonist at neuronal 5-hydroxytryptamine receptors. *Naunyn-Schmiedebergs Arch. Pharmac.* **326:** 36–44.

Fozard J. R. and Gittos M. W. (1983) Selective blockade of 5-hydroxytryptamine neuronal receptors by benzoic acid esters of tropine. *Br. J. Pharmac.* **80:** 511P.

Fozard J. R. and Host M. (1982) Selective inhibition of the Bezold–Jarisch effect of 5-HT in the rat by antagonists at neuronal 5-HT receptors. *Br. J. Pharmac.* **77:** 520P.

Fozard J. R. and Mobarok Ali A. T. M. (1978a) Receptors for 5-hydroxytryptamine on the sympathetic nerves of the rabbit heart. *Naunyn-Schmiedebergs Arch. Pharmac.* **301:** 223–235.

Fozard J. R. and Mobarok Ali A. T. M. (1978b) Blockade of neuronal tryptamine receptors by metoclopramide. *Eur. J. Pharmac,* **49:** 109–112.

Fozard J. R., Mobarok Ali A. T. M. and Newgrosh G. (1979) Blockade of serotonin receptors on autonomic neurones by (−)-cocaine and some related compounds. *Eur. J. Pharmac.* **59:** 195–210.

Fozard J. R. and Muscholl E. (1977) Presynaptic tryptamine receptors and responses to electrical stimulation of the cardiac sympathetic nerves. *Naunyn-Schmiedebergs Arch. Pharmac.* **297:** R50.

Fozard J. R. and Mwaluko G. M. P. (1976) Mechanism of the indirect sympathomimetic effect of 5-hydroxytryptamine on the isolated heart of the rabbit. *Br. J. Pharmac.* **57:** 115–125.

Freeman W. K., Rorie D. K. and Tyce G. M. (1981) Effects of 5-hydroxytryptamine on neuroeffector junction in human pulmonary artery. *J. appl. Physiol.* **51:** 693–698.

Furness J. B. and Costa M. (1980) Types of nerves in the enteric nervous system. *Neuroscience* **5:** 1–20.

Gaddum J. H. (1953) Tryptamine receptors. *J. Physiol., Lond.* **119:** 363–368.

Gaddum J. H. and Hameed K. A. (1954) Drugs which antagonize 5-hydroxytryptamine. *Br. J. Pharmac.* **9:** 240–248.

Gaddum J. H. and Picarelli Z. P. (1957) Two kinds of tryptamine receptor. *Br. J. Pharmac.* **12:** 323–328.

Garattini S. and Valzelli L. (1965) *Serotonin.* Elsevier, Amsterdam.

Gerschenfeld H. M., Paupardin-Tritsch D. and Deterre P. (1981) Neuronal responses to serotonin: a second view. In: *Serotonin Neurotransmission and Behaviour* (Jacobs B. L. and Gelperin A., Eds), pp. 105–130. MIT Press, Cambridge, Mass.

Gershon M. D. (1981) The enteric nervous system. *A. Rev. Neurosci.* **4:** 227–272.

Gershon M. D., Dreyfus C. F. and Rothman T. P. (1979) The mammalian enteric nervous system: A third autonomic division. In: *Trends in Autonomic Pharmacology* (Kalsner S., Ed.), Vol. I, pp. 59–101. Urban & Schwarzenberg, Baltimore, Munich.

Gintzler A. R. and Musacchio J. M. (1974) Interaction between serotonin and morphine in the guinea-pig ileum. *J. Pharmac. exp. Ther.* **189:** 484–492.

Ginzel K. H. and Kottegoda S. R. (1954) The action of 5-hydroxytryptamine and tryptamine on aortic and carotid sinus receptors in the cat. *J. Physiol., Lond.* **123:** 277–288.

Göthert M. (1982) Modulation of serotonin release in the brain via presynaptic receptors. *Trends Pharmac. Sci.* **3:** 437–440.

Göthert M. and Dührsen V. (1979) Effects of 5-hydroxytryptamine and related compounds on the sympathetic nerves of the rabbit heart. *Naunyn-Schmiedebergs Arch. Pharmac.* **308:** 9–18.

Guzman F., Braun C. and Lim R. K. S. (1962) Visceral pain and the pseudo-affective response to intra-arterial injection of bradykinin and other algesic agents. *Archs int. Pharmacodyn. Ther.* **136:** 353–384.

Gyermek L. (1962) Action of 5-hydroxytryptamine on the urinary bladder of the dog. *Archs int. Pharmacodyn. Ther.* **87:** 137–144.

Gyermek L. (1966) Drugs which antagonize 5-hydroxytryptamine and related indolealkylamines. In: *Handbuch der Experimentellen Pharmakologie. XIX 5-Hydroxytryptamine and Related Indolealkylamines* (Ersparmer V., Ed.), pp. 471–528. Springer, Berlin.

Gyermek L. and Bindler E. (1962a) Action of indole alkylamines and amidines on the inferior mesenteric ganglion of the cat. *J. Pharmac. exp. Ther.* **138:** 159–164.

Gyermek L. and Bindler E. (1962b) Blockade of the ganglionic stimulant action of 5-hydroxytryptamine. *J. Pharmac. exp. Ther.* **135:** 344–348.

Haefely W. (1972) Electrophysiology of the adrenergic neurone. In: *Handbook of Experimental Pharmacology.* Vol. 23 *Catecholamines* (Blaschko H. and Muscholl E., Eds), pp. 661–725. Springer, Berlin.

Haefely W. (1974) The effects of 5-hydroxytryptamine and some related compounds on the cat superior cervical ganglion *in situ. Naunyn-Schmiedebergs Arch. Pharmac.* **281:** 145–165.

Higashi H. (1977) 5-Hydroxytryptamine receptors on visceral primary afferent neurones in the nodose ganglion of the rabbit. *Nature* **267:** 448–450.

Higashi H. and Nishi S. (1982) 5-Hydroxytryptamine receptors of visceral primary afferent neurones on rabbit nodose ganglia. *J. Physiol., Lond.* **323:** 543–567.

Higashi H., Ueda N., Nishi S., Gallagher J. P. and Shinnick-Gallagher P. (1982) Chemoreceptors for serotonin (5-HT), acetylcholine (ACH), bradykinin (BK), histamine (H) and γ-aminobutyric acid (GABA) on rabbit visceral afferent neurons. *Brain Res. Bull.* **8:** 23–32.

Hirst G. D. S. and Silinsky E. M. (1975) Some effects of 5-hydroxytryptamine, dopamine and noradrenaline on neurones in the submucous plexus of guinea-pig small intestine. *J. Physiol., Lond.* **251:** 817–832.

Hong E. and Pardo E. G. (1966) On the pharmacology of 2-(1-piperazinyl)quinoline. *J. Pharmac. exp. Ther.* **153:** 259–265.

Huidobro-Toro J. P. and Foree B. (1980) Dual agonist–antagonist effects of 5-hydroxytryptamine (5-HT) in the guinea pig ileum: Evidence for a selective receptor desensitization effect. *Eur. J. Pharmac.* **61:** 335–345.

Humphrey P. P. A. (1983) Pharmacological classification of cardiovascular 5-hydroxytryptamine receptors. In: *Vascular Neuroeffector Mechanisms: 4th Intl. Symposium* (Bevan J. A. *et al.*, Eds), pp. 237–242. Raven Press, New York.

Humphrey P. P. A., Feniuk W. and Watts A. D. (1983) Prejunctional effects of 5-hydroxytryptamine on noradrenergic nerves in the cardiovascular system. *Fedn Proc. Fedn Am. Socs exp. Biol.* **42:** 218–222.

Ireland S. J., Fortune D. H. and Tyers M. B. (1983) Influence of 5HT uptake on the 5HT antagonist activity of metoclopramide on the rat superior cervical ganglion. *Br. J. Pharmac.* **78:** 68P.

Ireland S. J., Straughan D. W. and Tyers M. B. (1982) Antagonism by metoclopramide and quipazine of 5-hydroxytryptamine-induced depolarisations of rat isolated vagus nerve. *Br. J. Pharmac.* **75:** 16P.

Jacobs L. and Comroe J. H. Jr (1971) Reflex apnea, bradycardia, and hypotension produced by serotonin and phenyldiguanide acting on the nodose ganglia of the cat. *Circulation Res.* **24:** 145–155.

Jacobs J. and Poite-Bevierre M. (1960) Actions de la serotonine et de la benzyl-1-dimethyl-2,5-serotonine sur le coeur isole de lapin. *Archs int. Pharmacodyn. Ther.* **127:** 11–26.

Johnson S. M., Katayama Y. and North R. A. (1980) Multiple actions of 5-hydroxytryptamine on myenteric neurones of the guinea-pig ileum. *J. Physiol., Lond.* **304:** 459–470.

Johnson S. M., Katayama Y., Morita K. and North R. A. (1981) Mediators of slow synaptic potentials in the myenteric plexus of the guinea-pig ileum. *J. Physiol., Lond.* **320:** 175–186.

Kadzielawa K. (1983) Antagonism of the excitatory effects of 5-hydroxytryptamine on sympathetic preganglionic neurones and neurones activated by visceral afferents. *Neuropharmacology* **22:** 19–27.

Kalkman H. O., Harms Y. M., Van Gelderen E. M., Batink H. D., Timmermans P. B. M. W. M. and Van Zwieten P. A. (1983) Hypotensive activity of serotonin antagonists: correlation with α_1-adrenoceptor and serotonin receptor blockade. *Life Sci.* **32:** 1499–1505.

Kamikawa Y. and Shimo Y. (1983) Indirect action of 5-hydroxytryptamine on the isolated muscularis mucosae of the guinea-pig oesophagus. *Br. J. Pharmac.* **78:** 103–110.

Kilbinger H., Kruel R., Pfeuffer-Friederich I. and Wessler I. (1982) The effects of metoclopramide on acetylcholine release and on smooth muscle response in the isolated guinea-pig ileum. *Naunyn-Schmiedebergs Arch. Pharmac.* **319:** 231–238.

Kilbinger H. and Pfeuffer-Friederich I. (1982) Facilitation and inhibition by serotonin of acetylcholine release from guinea-pig myenteric plexus: evidence for two types of neuronal serotonin receptors. *Naunyn-Schmiedebergs Arch. Pharmac.* **319:** R59.

Kimura T. and Satoh S. (1983) Presynaptic inhibition by serotonin of cardiac sympathetic transmission in dogs. *Clin. exp. Pharmac. Physiol.* **10:** 535–542.

Kiraly M., Ma R. C. and Dun N. J. (1983) Serotonin mediates a slow excitatory potential in mammalian celiac ganglia. *Brain Res.* **275:** 378–383.

Krayer O. (1961) The history of the Bezold–Jarisch effect. *Naunyn-Schmiedebergs Arch. Pharmac.* **240:** 361–368.

Kubo T. and Su C. (1983) Effects of serotonin and some other neurohumoral agents on adrenergic neurotransmission in spontaneously hypertensive rat vasculature. *Clin. exp. Hypert.* **A5:** 1501–1510.

Lansdown M. J. R., Nash H. L., Preston P. R., Wallis D. I. and Williams R. G. (1980) Antagonism of 5-hydroxytryptamine receptors by quipazine. *Br. J. Pharmac.* **68:** 525–532.

Lewis G. P. (1960) The inhibition by morphine of the action of smooth muscle stimulants on the guinea pig intestine. *Br. J. Pharmac.* **15:** 425–431.

Leysen J. (1984) Problems in *in vitro* receptor binding

studies and identification and role of serotonin receptor sites. *Neuropharmacology* **23:** 247–254.

Lindahl O. (1961) Experimental skin pain induced by injection of water-soluble substances in humans. *Acta physiol. scand.* **51:** 1–90.

McCall R. B. (1983) Serotonergic excitation of sympathetic preganglionic neurones: A microiontophoretic study. *Brain Res.* **289:** 121–127.

McCall R. B. and Aghajanian G. K. (1979) Serotonergic facilitation of facial motoneuron excitation. *Brain Res.* **169:** 11–27.

McCall R. B. and Aghajanian G. K. (1980) Pharmacological characterization of serotonin receptors in the facial motor nucleus: a microiontophoretic study. *Eur. J. Pharmac.* **65:** 175–183.

McGrath M. A. (1977) 5-Hydroxytryptamine and neurotransmitter release in canine blood vessels. Inhibition by low and augmentation by high concentrations. *Circulation Res.* **41:** 428–435.

McGrath M. A. and Shepherd J. T. (1976) Inhibition of adrenergic neurotransmission in vascular smooth muscle by 5-hydroxytryptamine. *Circulation* **54:** 11–20.

McGrath M. A. and Shepherd J. T. (1978) Histamine and 5-hydroxytryptamine-inhibition of transmitter release mediated by H_2- and 5-hydroxytryptamine receptors. *Fedn Proc. Fedn Am. Socs exp. Biol.* **37:** 195–198.

Martinez A. A. and Lokhandwala M. F. (1980) Evidence for a presynaptic inhibitory action of 5-hydroxytryptamine on sympathetic neurotransmission to the myocardium. *Eur. J. Pharmac.* **63:** 303–311.

Mense S. and Schmidt R. F. (1974) Activation of group IV afferent units from muscle by algesic agents. *Brain Res.* **72:** 305–310.

Müller-Schweinitzer E. (1981) Agonist potencies of tryptamine derivatives at pre- and postjunctional receptors in canine saphenous vein. *Postgrad. med. J.* **57:** 36–44.

Nash H. L. and Wallis D. I. (1981) Effects of divalent cations on responses of a sympathetic ganglion to 5-hydroxytryptamine and 1,1-dimethyl-4-phenyl piperazinium. *Br. J. Pharmac.* **73:** 759–772.

Neild T. O. (1981) The action of 5-hydroxytryptamine and possible 5-hydroxytryptamine antagonists on neurones of the guinea-pig submucous plexus. *Gen. Pharmac.* **12:** 281–284.

Neto F. R. (1978) The depolarizing action of 5-HT on mammalian non-myelinated nerve fibres. *Eur. J. Pharmac.* **49:** 351–356.

North R. A. (1982) Electrophysiology of the enteric nervous system. *Neuroscience* **7:** 315–325.

North R. A., Henderson G., Katayama Y. and Johnson S. M. (1980) Electrophysiological evidence for presynaptic inhibition of acetylcholine release by 5-hydroxytryptamine in the enteric nervous system. *Neuroscience* **5:** 581–586.

Page I. H. (1958) Serotonin (5-hydroxytryptamine); the last four years. *Physiol. Rev.* **38:** 277–335.

Paintal A. S. (1973) Vagal sensory receptors and their reflex effects. *Physiol. Rev.* **53:** 159–227.

Parry O. and Roberts M. H. T. (1980) The responses of motor neurones to 5-hydroxytryptamine. *Neuropharmacology* **19:** 515–518.

Peroutka S. J. and Snyder S. H. (1979) Multiple serotonin receptors: differential binding of [^{3}H] 5-hydroxytryptamine, [^{3}H] lysergic acid diethylamide and [^{3}H] spiroperidol. *Molec. Pharmac.* **16:** 687–699.

Pfeuffer-Friederich I. and Kilbinger H. (1983) LSD induced inhibition of evoked acetylcholine release from guinea-pig myenteric plexus is mediated through serotonin (5-HT) receptors. *Naunyn-Schmiedebergs Arch. Pharmac.* **324:** R10.

Phillis J. W., Tebecis A. K. and York D. H. (1968) Depression of spinal motoneurones by noradrenaline, 5-hydroxytryptamine and histamine. *Eur. J. Pharmac.* **4:** 471–475.

Rocha e Silva M., Valle J. R. and Picarelli Z. P. (1953) A pharmacological analysis of the mode of action of serotonin (5-hydroxytryptamine) upon the guinea-pig ileum. *Br. J. Pharmac.* **8:** 378–388.

Salmoiraghi G. C., Page I. H. and McCubbin J. W. (1956) Cardiovascular and respiratory response to intravenous serotonin in rats. *J. Pharmac. exp. Ther.* **118:** 477–481.

Sampson S. R. and Jaffe R. A. (1975) Excitatory effects of 5-hydroxytryptamine, veratridine and phenyl diguanide on sensory ganglion cells of the nodose ganglion of the cat. *Life Sci.* **15:** 2157–2165.

Sato T., Takayanagi I. and Takagi K. (1974) Effects of acetylcholine-releasing drugs on electrical activities obtained form Auerbach's plexus in the guinea-pig ileum. *Jap. J. Pharmac.* **12:** 115–118.

Saum W. R. and De Groat W. C. (1973) The actions of 5-hydroxytryptamine on the urinary bladder and on vesical autonomic ganglia in the cat. *J. Pharmac. exp. Ther.* **185:** 70–83.

Sicuteri F., Fanciullacci M., Franchi G. and Del Biancho P. L. (1965) Serotonin-bradykinin potentiation on the pain receptors in man. *Life Sci.* **4:** 309–316.

Simonds W. F. and De Groat W. C. (1980) Antagonism by picrotoxin of 5-hydroxytryptamine-induced excitation of primary afferent neurons. *Brain Res.* **192:** 592–597.

Sinha Y. K. and West G. B. (1953) The antagonism between local anaesthetic drugs and 5-hydroxytryptamine. *J. Pharm. Pharmac.* **5:** 370–374.

Stansfeld C. E. and Wallis D. I. (1982) A- and C-type cells of the rabbit nodose ganglion respond differently to 5-HT, GABA and dimethylphenylpiperazinium DMPP. *J. Physiol., Lond.* **328:** 14P–15P.

Trendelenburg U. (1967) Some aspects of the pharmacology of autonomic ganglion cells. *Ergebn. Physiol.* **59:** 1–85.

VanderMaelen C. P. and Aghajanian G. K. (1980) Intracellular studies showing modulation of facial motoneuron excitability by serotonin. *Nature* **287:** 346–347.

VanderMaelen C. P. and Aghajanian G. K. (1982a) Serotonin-induced depolarization of rat facial motor neurons *in vivo*: comparison with amino acid transmitters. *Brain Res.* **239:** 139–152.

VanderMaelen C. P. and Aghajanian G. K. (1982b) Intracellular studies on the effects of systemic administration of serotonin agonists on rat facial motor neurons. *Eur. J. Pharmac.* **78:** 233–236.

Vane J. R. (1959) The relative activities of some tryptamine analogues on the isolated rat stomach strip preparation. *Br. J. Pharmac.* **14:** 87–98.

Vanov S. (1965) Responses of the rat urinary bladder *in situ* to drugs and to nerve stimulation. *Br. J. Pharmac.* **24:** 591–600.

Wallis D. I. (1979) The apparent multiplicity of ganglionic receptors. In: *Trends in Autonomic Pharmacology* (Kalsner S., Ed.), Vol. I, pp. 21–57. Urban & Schwarzenberg, Baltimore, Munich.

Wallis D. (1981) Neuronal 5-hydroxytryptamine receptors outside the central nervous system. *Life Sci.* **29:** 2345–2355.

Wallis D. I. and Nash H. L. (1980) The action of methylated derivatives of 5-hydroxytryptamine at ganglionic receptors. *Neuropharmacology* **19:** 465–472.

Wallis D. and Nash H. (1981) Relative activities of substances related to 5-hydroxytryptamine as depolarizing agents of superior cervical ganglion cells. *Eur. J. Pharmac.* **70:** 381–392.

Wallis D. I. and North R. A. (1978) The action of 5-hydroxytryptamine on single neurones of the rabbit superior cervical ganglion. *Neuropharmacology* **17:** 1023–1028.

Wallis D. I., Stansfeld C. E. and Nash H. L. (1982)

depolarizing responses recorded from nodose ganglion cells of the rabbit evoked by 5-hydroxytryptamine and other substances. *Neuropharmacology* **21:** 31–40.

Wallis D. I., Williams C. and Wali F. A. (1978) The effect of 5-hydroxytryptamine and hexamethonium on post-train facilitation in the superior cervical ganglion. *Eur. J. Pharmac.* **52:** 17–25.

Wallis D. I. and Woodward B. (1975) Membrane potential changes induced by 5-hydroxytryptamine in the rabbit superior cervical ganglion. *Br. J. Pharmac.* **55:** 199–212.

Watts A. D., Feniuk W. and Humphrey P. P. A. (1981) A pre-junctional action of 5-hydroxytryptamine and methysergide on noradrenergic nerves in dog isolated saphenous vein. *J. Pharm. Pharmac.* **33:** 515–520.

Weight F. F. and Swenberg C. E. (1981) Serotonin and synaptic mechanisms in sympathetic neurons. In: *Serotonin Neurotransmission and Behaviour* (Jacobs B. L. and Gelperin A., Eds), pp. 131–155. MIT Press, Cambridge, Mass.

Weinstock M. and Schechter Y. (1975) Antagonism by propranolol of the ganglion stimulant action of 5-hydroxytryptamine. *Eur. J. Pharmac.* **32:** 293–301.

White S. R. and Neuman R. S. (1980) Facilitation of spinal motoneurone excitability by 5-hydroxytryptamine and noradrenaline. *Brain Res.* **188:** 119–127.

White S. R. and Neuman R. S. (1983) Pharmacological antagonism of facilitatory but not inhibitory effects of serotonin and norepinephrine on excitability of spinal motor neurons. *Neuropharmacology* **22:** 489–494.

Wood J. D. and Mayer C. J. (1978) Slow synaptic excitation mediated by serotonin in Auerbach's plexus. *Nature* **276:** 836–837.

Wood J. D. and Mayer C. J. (1979) Serotonergic activation of tonic-type enteric neurons in guinea pig small bowel. *J. Neurophysiol.* **42:** 582–593.

Wurzel M. (1966) Serotonin receptor in rabbit artery. *Am. J. Physiol.* **211:** 1424–1428.

Yamaguchi T. (1972) Effects of 5-hydroxytryptamine on isolated strips of the guinea-pig stomach. *Br. J. Pharmac.* **44:** 100–108.