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REVIEW

The animal pharmacology of drugs used in the treatment of migraine

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In a disease such as migraine one might question the relevance of "The animal pharmacology of drugs used therapeutically in migraine" for several reasons. Firstly, because so far as we know, experimental animals do not suffer from migraine. Secondly, because such animal experimental models as have been designed have the inevitable disadvantage that the condition they purport to represent is itself only poorly understood. Finally, the historical record is less than encouraging since at least two of the most effective drugs in current migraine therapy (ergotamine and methysergide) were introduced originally on the strength of pharmacological properties in animals now considered irrelevant to their antimigraine action (Saxena, 1974; Saxena & de Vlaam-Schluter, 1974).

Nevertheless, drugs have come into use which benefit the migraine sufferer either when given during an acute attack or when administered prophylactically. With the possible exception of ergotamine, however, the precise mechanism of their antimigraine action remains obscure. Here, I feel, is the justification for animal studies, since an increase in knowledge can only result from continuing intensive study of the pharmacological effects of these drugs in animals or on isolated tissues. It is possible that the pharmacological properties of the therapeutically useful drugs which bestow protection in migraine have already been observed in animal experiments but that we have not yet recognized them as such. The purpose of this review is to describe these properties and in particular to emphasize those most likely to be clinically significant.

DRUGS IN USE AND SCOPE OF THE REVIEW

Table 1 indicates the drugs which could qualify for inclusion in this review, the first half of Table 1 includes those in regular therapeutic use. The second half lists those drugs with proven efficacy in migraine but not at this stage in regular therapeutic use. Clearly some limitation is appropriate, and I have decided to exclude all the drugs listed in the second half, and those drugs in the first half which are specifically antiemetic or are assumed to act by alleviation of secondary stress symptoms. In practice, this leaves ergotamine (+ caffeine), dihydroergotamine, and the antipyretic analgesics (deliberately included because of the potential importance of their effects on prostaglandin synthetase) as drugs for the acute attack, and dihydroergotamine, clonidine, methysergide, cyproheptadine and pizotifen for use prophylactically.

Two further considerations have helped define the scope of this review. First, prominence will be given to those drug properties which can be interpreted in terms of the known vascular nature of the condition and the putative role of naturally-occurring vasoactive substances such as 5-hydroxytryptamine (5-HT). Secondly, particular

emphasis will be laid on those properties manifested at doses or concentrations within the therapeutic range. This latter presents some difficulties for the reviewer since, although effective dose regimes of antimigraine drugs are well established (Table 2), little or no information is available regarding plasma concentrations during therapy.

Table 1. *Drugs commonly employed in the treatment of migraine (Wilkinson 1971; Lance, 1973) and compounds with demonstrable anti-migraine effects but not in regular therapeutics use.*

Drugs commonly employed		*Compounds with antimigraine effects*	
Acute attack		Compound	Reference
Antipyretic analgesics:		Folic acid	A Kopjas (1969)
Aspirin		Indomethacin	A Nelemans (1971)
Paracetamol		Amitryptiline	P Gomersall & Stuart (1973)
Anti-emetics:		Anticholinesterases	P Ikonomoff (1968)
Cyclizine		Propranolol	P Widerøe and Vigander (1974)
Metoclopramide		Dimethothiazine	P Foldes (1972)
Thiethylperazine		Dipyridamol	P Barcia (1970)
Selectively antimigraine:		Flumedroxone	P Lundberg (1969)
Ergotamine (+ caffeine)		5-Hydroxytryptophan	P Sicuteri (1972)
Dihydroergotamine		Oestradiol	P Somerville (1972)
Prophylaxis		Oral contraceptives (various)	P Larsson-Cohn & Lundberg (1970)
Hypnotics and tranquillizers:		Opipramol	P Jacobs (1972)
Barbiturates		Progesterone	P Greene & Dalton (1953)
Diazepam		Phenelzine	P Anthony & Lance (1969)
Chlorpromazine			
Prochlorperazine			
Selectively antimigraine:			
Methysergide			
Pizotifen			
Cyproheptadine			
Dihydroergotamine			
Clonidine			

A = Acute attack
P = Prophylactic

Table 2. *The therapeutic doses of antimigraine drugs.*

		Acute attack		Prophylaxis	
Drug	Route	Dose (mg)	Dose ($\mu g\ kg^{-1}$)	Daily dose (mg)	Daily dose ($\mu g\ kg^{-1}$)
Ergotamine tartrate	by inhalation	0·36–0·72	5·1–10		
	intramuscularly	0·25–0·5	3·6–7·1		
	orally	0·5–2	7·1–29		
	rectally				
Caffeine	orally	100–200	1430–2870		
Dihydroergotamine mesylate	intramuscularly	1–2	14–29		
	orally	2–3	29–43	3–6	43–86
Aspirin	orally	300–1200	4290–17140		
Paracetamol	orally	550–1100	7870–15710		
Clonidine hydrochloride	orally			0·1–0·15	1·4–2·1
Methysergide hydrogen maleate	orally			2–6	29–86
Pizotifen	orally			4·5–9	64–129
Cyproheptadine hydrochloride	orally			12–24	171–343

Hence, all *in vitro* work lacks the relevant therapeutic reference points, and even the *in vivo* studies suffer similar problems. Thus, pharmacologists have a habit of administering drugs locally to specific tissues in ways which defy expression in terms of body weight. Further, there is the perennial problem of relating effects obtained in acute experiments to the prophylactic situation where low doses of drugs are ingested for long periods of time. For these reasons the properties to be described in this review have been classified as occurring at low, medium or high doses or concentrations. Clearly, the effects likely to be clinically important would be expected to lie within the low, and exceptionally, the medium categories. The effects observed at high doses will be regarded as being therapeutically irrelevant.

1. DRUGS USEFUL IN THE ACUTE ATTACK

A. ERGOTAMINE

(i) *Low dose/concentration effects*

The minimum dose of ergotamine required to produce a pharmacological response *in vivo* is about 1 μg kg^{-1} injected intravenously. Within the therapeutic range (3 to 14 μg kg^{-1}) four basic properties have been described. These are sensitization of smooth muscle to various stimulation procedures, peripheral vasoconstriction, antagonism of 5-hydroxytryptamine vasoconstrictor responses and inhibition of reflex vasodilatation evoked by increased baroreceptor activity.

(a) *Sensitisation of smooth muscle.* In the spinal cat, intravenous injections of 1 to 5 μg kg^{-1} of ergotamine increased the contractile response of the nicitating membrane to sympathetic nerve stimulation and to injections of 5-hydroxytryptamine, tyramine, adrenaline and noradrenaline (Salzmann, Pacha, & others, 1968). Similar doses of ergotamine enhanced the blood pressure responses to adrenaline and noradrenaline in spinal cats (Weidmann & Taeschler, 1966; Salzmann & others, 1968) and dogs (Wellens, 1964; Wellens & Wauters, 1966b). In *in vitro* experiments, sensitization of smooth muscle to sympathetic stimulation and stimulant drugs has been observed with extremely low concentrations of ergotamine on the perfused cat spleen (Salzmann & others, 1968) and rabbit auricular artery (Carroll, Ebeling & Glover, 1972; Carroll & Glover, 1973). Such a generalized sensitization cannot be explained by inhibition of monoamine tissue uptake mechanisms as has been suggested (Salzmann & others, 1968; Salzmann & Kalberer, 1973) for a number of reasons. Firstly, the stimulant effects of both direct and indirect sympathomimetic amines on the cat nictitating membrane were potentiated (Weidmann & Taeschler, 1966; Salzmann & others, 1968). Secondly the stimulant action of histamine, a diamine, on the perfused rabbit auricular artery (Carroll & others, 1972) was also strongly enhanced by ergotamine. Finally, although quantitative comparisons are difficult, inhibition of monoamine uptake can only be demonstrated at concentrations of ergotamine greater than those causing sensitization (Dengler, Spiegel & Titus, 1961; Salzmann & others, 1968; Lingjaerde, 1970; Salzmann & Kalberer, 1973), if at all (Fozard & Berry, 1974). A more plausible explanation has been advanced by Weidmann & Taeschler (1966), based on the observations that ergotamine in higher concentrations stimulates those preparations in which an enhancement of stimulation is seen. Their proposal that subthreshold stimulatory effects of ergotamine achieve threshold or greater levels in the presence of other stimulant agents or procedures seems reasonable. An identical mechanism has been proposed to explain the sensitization resulting from the interaction of 5-hydroxytryptamine and vasoconstrictor agents on the rabbit auriculary artery (Fozard, 1973).

(b) *Peripheral vasoconstriction.* Intravenous injections of ergotamine between 1 and 10 $\mu g\ kg^{-1}$ cause significant dose-related increases in arterial pressure in cats (Cerletti, Berde, & others, 1960) and dogs (Carpi & Virno, 1957; Cerletti & others, 1960; Wellens & Wauters, 1966a; Saxena & de Vlaam-Schluter, 1974). The effects are particularly long lasting and result from a widespread increase in peripheral resistance (Cerletti & others, 1960; Weidmann & Taeschler, 1966; Wellens & Wauters, 1966a, b; Saxena & de Vlaam-Schluter, 1974). In experiments in dogs, evidence has been obtained for a selective vasoconstrictor effect of ergotamine in the carotid artery bed. Thus Carpi & Virno (1957) demonstrated a more marked vasoconstriction in the cerebral vessels than the vessels of the nose or kidney. Saxena & de Vlaam-Schluter (1974) extended these observations to include the whole of the carotid artery bed and the vasculature supplied by the femoral, superior mesenteric, renal, vertebral and coronary arteries. Their results clearly indicated a selective vasoconstrictor effect of ergotamine on the carotid artery bed which was especially evident at the lowest doses used (1 to 2 $\mu g\ kg^{-1}$ intravenously) and when the carotid vasculature was artificially dilated. There are several possible reasons for the selective vasoconstrictor action of ergotamine. One is the possibility that after intravenous injection different amounts of drug will arrive at the active sites due to differences in regional blood flow and degrees of dilution. Another may be the pre-existing vascular tone of the particular region which Aellig (1967) has shown can determine whether ergotamine evokes vasoconstriction or vasodilation. Ergotamine also possesses a certain degree of selectivity for various types of vascular tissue. For example, on the skeletal muscle vasculature of the cat hind limb, ergotamine has a highly selective effect on the capacitance vessels and minimal effects on the resistance vessels (Owen, 1971), whereas in the skin, ergotamine constricts both resistance and capacitance vessels (Owen & Stürmer, 1972). Whatever the ultimate explanation for the relative selectivity turns out to be, the fact remains that constriction of peripheral blood vessels and especially those of the dilated carotid artery bed is an established feature of low concentrations of ergotamine within the therapeutic range.

Vasoconstriction with ergotamine *in vivo* is due to a direct action predominantly, but not exclusively, on α-adrenoceptors, because it is markedly but not always completely inhibited by low concentrations of phenoxybenzamine or phentolamine (Innes, 1962a; Weidmann & Taeschler, 1966; Saxena & de Vlaam-Schluter, 1974; Vargaftig & Lefort, 1974), yet unaffected by depletion of noradrenaline stores (Osswald, Guimaraes & Garrett, 1970). The situation *in vitro* is similar. Low concentrations of ergotamine readily constrict isolated segments of arteries (Innes, 1962a; Carroll & others, 1972; Carroll & Glover, 1973) and veins (Guimaraes & Osswald, 1969; Müller-Schweinitzer & Stürmer, 1974; Müller-Schweinitzer, 1974a) by a direct action on α-adrenoceptors. In dog femoral and saphenous vein strips, however, an additional vasoconstrictor mechanism has been observed (Müller-Schweinitzer, 1974a). Further investigation of this phenomenon has disclosed an increase in the resting output of a prostaglandin E-like material from the vein during incubation with ergotamine (10 ng ml^{-1}) and an inhibitory effect on the contractile response to ergotamine by the prostaglandin synthetase inhibitor, indomethacin (Müller-Schweinitzer, 1974a). These results suggest that whilst the vasoconstrictor activity of ergotamine is mediated mainly through α-adrenoceptors, enhanced synthesis of prostaglandin E-like substance(s) may also contribute. It remains to be established whether this interesting property is a characteristic of ergotamine (or dihydroergotamine—Müller-Schweinitzer, 1974b) *per*

se or simply a feature of drugs which cause the vein to contract. Cell membrane disturbance, and this must surely occur during venous contraction, is claimed to be a potent stimulant of prostaglandin synthesis and release (Piper, 1973).

(c) *Antagonism of 5-hydroxytryptamine vasoconstrictor responses.* Intravenous injections of 1 to 20 μg kg^{-1} of ergotamine inhibited pressor responses to 5-HT in dogs and cats (Wellens & Wauters, 1966a) and abolished or reversed vasoconstrictor responses to 5-hydroxytryptamine in the dog hind limb (Wellens & Wauters, 1966b) and carotid artery bed (Saxena & de Vlaam-Schluter, 1974). These effects were selective in that responses to other vaso-active drugs were unaffected or even enhanced under identical experimental conditions. *In vitro* investigations have amply confirmed these *in vivo* observations. Thus, low concentrations of ergotamine selectively antagonized 5-hydroxytryptamine on the vessels of the rabbit ear (Gaddum & Hameed, 1954), rabbit hind limb (Meier, Tripod & Wirz, 1957) and segments of rabbit auricular artery (Carroll & others, 1972). It is of wider significance that much higher concentrations of ergotamine were required to inhibit the stimulant effects of 5-hydroxtryptamine on extravascular smooth muscle such as that of the bronchi, nictitating membrane or intestine (Gaddum & Hameed, 1954; Bhattacharya, 1955; Salzmann & others, 1968). The reverse situation seems to prevail for the more classical 5-hydroxytryptamine D receptor antagonists methysergide and cyproheptadine (sections 2A and 2C below). The results emphasise the fundamental differences that exist between 5-hydroxytryptamine D receptors at different sites in the body. Saxena, Houwelingen & Bonta (1971), Saxena (1972) and Bakhle & Smith (1974b) have already drawn attention to the existence of similar differences within different parts of the peripheral vascular tree.

(d) *Inhibition of reflex baroreceptor vasodilation.* Peripheral vasodilation is observed in the hind limb of anaesthetized dogs following intravenous injections of noradrenaline sufficient to raise systemic blood pressure. The vasodilation is due to vasomotor centre inhibition arising from reflex baroreceptor activity (Wellens, 1964; Wellens & Wauters, 1966b). Ergotamine, 1 to 10 μg kg^{-1} injected intravenously inhibited the vasodilator reflex, and in cross-circulation experiments the site of inhibition was unequivocally shown to be peripheral (Wellens, 1964).

(ii) *Medium dose/concentration effect*

I have included only one pharmacological property in this section and that is the inhibitory effect of ergotamine on the carotid occlusion reflex. Two factors are responsible for the rise in pressure following occlusion of one or both carotid arteries. One is the reduction in baroreceptor impulses owing to the reduced pressure in the region above the point of clamping. The second is the increased chemoreceptor activity resulting from the hypoxic conditions which develop within the carotid body when the normal blood flow is reduced during clamping. Doses of ergotamine between 2 and 10 times larger than those producing the effects in the preceding section inhibited the baroreceptor component of the rise in blood pressure evoked by carotid occlusion in the cat (Euler & Schmitterlöw, 1944; Cerletti & others, 1960) and dog (Saxena & de Vlaam-Schluter, 1974), but had no effect on the vasomotor drive evoked by activation of chemoreceptors (Euler & Schmitterlöw, 1944). The site of baroreceptor reflex inhibition is assumed to be central (Euler & Schmitterlöw, 1944; Saxena & de Vlaam-Schluter, 1974).

Despite the inhibitory effects on baroreceptor reflexes, ergotamine did not, even in high doses, affect the spontaneous central sympathetic outflow in either cats or dogs (Schmitt & Fénard, 1970). This observation is of more than passing interest in view of the potency of ergotamine at peripheral α-adrenoceptors and the evidence that α-adrenoceptors are present in the vasomotor centre which decrease the peripheral sympathetic outflow when activated (Section 2B below, Van Zwieten, 1973). The fact that clonidine in low concentrations inhibited the spontaneous vasomotor outflow in identical experiments to those in which large doses of ergotamine proved inactive emphasises a basic dissimilarity in their mechanism of action. It also reinforces the conclusions of Van Zwieten (1973) that the α-adrenoceptors mediating vasoconstriction in the periphery and those in the brain mediating vasomotor inhibition are probably different.

(iii) *High dose/concentration effects*

This section includes the effects of ergotamine on tryptamine-evoked pulmonary spasmogen release, on monoamine tissue uptake and storage mechanisms, its α-adrenoceptor blocking activity and its effects on neuronal transmitter release.

(a) *Inhibition of tryptamine evoked pulmonary spasmogen release.* Isolated perfused lungs of rats, guinea-pigs and dogs release a mixture of spasmogens including prostaglandins in response to infusions of amines including tryptamine and 5-hydroxytryptamine (Alabaster & Bakhle, 1970). These findings led to the hypothesis that attacks of migraine might be caused by an analogous release of active substances from the lungs which would then act on the cranial vasculature (Sandler, 1972). Following a suggestion contained in this hypothesis, Bakhle & Smith (1972) investigated the effect of ergotamine on amine-evoked pulmonary spasmogen release. They found that ergotamine (650 ng ml^{-1}) infused through rat lung completely suppressed the release of spasmogens evoked by activation of tryptamine receptors. Further, the effect was selective in that spasmogen release evoked by histamine or tyramine was unaffected (Bakhle & Smith, 1972).

(b) *Inhibition of monoamine uptake.* The inhibitory effects of ergotamine on noradrenaline and 5-hydroxytryptamine tissue uptake processes have been clearly demonstrated in *in vitro* experiments, but little evidence is available *in vivo*. In the cat spleen, infusion of 50 to 100 ng ml^{-1} of ergotamine increased by two to three times the noradrenaline output evoked by electrical stimulation of the sympathetic nerves (Salzmann & others, 1968). The suggestion that ergotamine was blocking noradrenaline tissue re-uptake is supported by the observation of Dengler (1961) that 500 ng ml^{-1} of ergotamine inhibited the accumulation of noradrenaline by cat spleen slices by 30%. The uptake of 5-hydroxytryptamine has also been reported to be inhibited by ergotamine although concentrations of 0·1 to 3 μg ml^{-1} were required in the perfused cat spleen (Salzmann & Kalberer, 1973) and the dose for 50% inhibition of uptake into platelets was 5 μg ml^{-1} (Lingjaerde, 1970). On the other hand, the uptake of 5-HT by the rabbit heart was actually enhanced during perfusion with 1 μg ml^{-1} of ergotamine (Fozard & Berry, 1974).

(c) *Inhibition of α-adrenoceptors.* To have included the α-adrenoceptor blocking action of ergotamine as a high dose effect without some reservations would be misleading since, in several isolated tissues, adrenolytic effects are prominent at very low

concentrations. However, *in vivo*, where reference to therapeutic dose levels is possible, 50 to 100 μg kg^{-1} (i.e. 10 to 15 times the therapeutic range) are the minimum doses for producing blockade of both vascular and extra-vascular smooth muscle stimulant responses to adrenaline and noradrenaline in cats (Innes, 1962a) and dogs (Wellens, 1964; Osswald & others, 1970; Saxena & de Vlaam-Schluter, 1974). Even with much higher doses (3 mg kg^{-1}) full blockade of catecholamine pressor responses may not be achieved (Pacha & Salzmann, 1970). In contrast, in *in vitro* experiments on dog isolated femoral and saphenous veins, ergotamine concentrations of 0·6 and 5·2 ng ml^{-1} caused a 2-fold antagonism of the response to noradrenaline (Guimaraes & Osswald, 1969; Müller-Schweinitzer & Stürmer, 1974), although a minimum of 40 ng ml^{-1} of ergotamine was required to block the effects of adrenaline in the perfused rabbit's ear (Gaddum & Hameed, 1954). The variable extent to which α-adrenoceptor responses appear to be inhibited by ergotamine undoubtedly reflects the mélange of pharmacological properties displayed by ergotamine at higher dose levels. *In vivo*, a combination of α-adrenoceptor stimulatory, reflex inhibitory and neuronal noradrenaline uptake inhibitory activity might well mask the α-adrenoceptor blocking activity.

(d) *Inhibition of autonomic neuronal transmitter release.* Ergotamine in high concentrations can inhibit the release of the sympathetic and parasympathetic transmitter substances. At a concentration of 10 μg ml^{-1} ergotamine inhibited both acetylcholine release from the cholinergic neurons of the guinea-pig ileum (Paton & Vizi, 1969) and noradrenaline release from the isolated spleen (Salzmann & others, 1968). It seems likely that ergotamine is stimulating the α-adrenoceptors suggested to be located on or near terminal sympathetic fibres (Starke, 1972) and parasympathetic neurons (Kosterlitz & Lees, 1972) which inhibit transmitter release when activated. Indeed, the prevention of the inhibitory effect of ergotamine by phentolamine (Paton & Vizi, 1969) would support this suggestion.

Clinical relevance

The wide spectrum of pharmacological activity displayed by ergotamine at relatively low dose levels makes it difficult to isolate any single property as being responsible for its clinical effectiveness. Nevertheless, the strongest candidate for such a role must be the persistent peripheral vasoconstriction which appears to be especially evident in the dilated carotid artery bed. Two of the other properties exhibited by ergotamine at low doses, potentiation of sympathetic nerve stimulation and vasoconstrictor agents and inhibition of depressor baroreceptor reflexes, could contribute significantly to this vasoconstriction.

Of the remaining properties, it is difficult to see a meaningful role for the potent antagonism displayed by ergotamine towards 5-hydroxytryptamine vasoconstrictor responses since, 5-hydroxytryptamine levels of platelet-rich plasma fall dramatically just before an attack (Curran, Hinterberger & Lance, 1965; Anthony, Hinterberger & Lance, 1967) and intravenous injections of 5-hydroxytryptamine can alleviate migraine (Anthony & others, 1967). The high doses or concentrations of ergotamine required to inhibit monoamine uptake, neuronal transmitter release and, in *in vivo* experiments, α-adrenoceptors, would indicate a minor role, if any, for these properties in the clinical situation. A minor role might also be accorded to inhibition of pulmonary spasmogen release which was demonstrated at a concentration of 650 ng ml^{-1}. However, the response obtained was maximal and it is possible that lower concentrations would

also have proved effective. In view of the potential importance of amine-evoked spasmogen release to migraine (see sections 1D and 2A below) the observation may well have therapeutic relevance.

B. DIHYDROERGOTAMINE

Hydrogenation of ergotamine to give dihydroergotamine results in changes in pharmacological activity which in the main are quantitative rather than qualitative. Thus, dihydroergotamine has less intrinsic vasoconstrictor activity than ergotamine, yet its inhibitory effects on the central nervous system, its facilitatory effects on the release of the sympathetic transmitter substance, and its α-adrenoceptor antagonist potency are all increased (Rothlin, 1946/47; Salzmann & others, 1968). This means in practice that most of the pharmacological profile of dihydroergotamine is in evidence within a narrow dose or concentration range. This not only makes a rigid categorization of its properties according to dosage unrealistic (which is the reason why only two sections are included below), but also increases the difficulty in deciding which of the pharmacological effects are clinically relevant.

(i) *Low and medium dose/concentration effects*

The threshold dose of dihydroergotamine to produce a pharmacological response *in vivo* is 5 to 20 $\mu g\ kg^{-1}$ injected intravenously. Within the therapeutic range (10 to 50 $\mu g\ kg^{-1}$) dihydroergotamine sensitizes vascular and extravascular smooth muscle to stimulant drugs, inhibits central vasomotor tone, evokes peripheral vasoconstriction and blocks α-adrenoceptors and vasoconstrictor responses to 5-hydroxytryptamine.

(a) *Sensitization of smooth muscle.* In the spinal cat, dihydroergotamine (10 to 20 $\mu g\ kg^{-1}$) strongly enhanced the contraction of the nictitating membrane evoked by stimulation of the sympathetic nerves, and both the blood pressure and nictitating membrane responses to injections of adrenaline, noradrenaline, tyramine and 5-hydroxytryptamine (Weidmann & Taeschler, 1966). Paradoxically, similar doses in anaesthetized cats inhibited the pressor effects of adrenaline (Rothlin, 1946). That sensitization can occur independently of an intact central nervous system is also suggested by results from *in vitro* experiments where dihydroergotamine, in low concentrations enhanced responses of the rabbit auricular artery to stimulant drugs (Carroll & others, 1972; Carroll & Glover, 1973).

(b) *Inhibition of central vasomotor tone and circulatory reflexes.* In marked contrast to ergotamine, whose effects on blood pressure are invariably pressor, intravenous injections of dihydroergotamine in anaesthetized dogs, cats and rabbits produce a fall in blood pressure accompanied by peripheral vasodilation (Rothlin, 1946; Konzett & Rothlin, 1953; Chu & Stürmer, 1973). The site of action is the vasomotor centre in the medulla (Konzett & Rothlin, 1953) and a decrease in the efferent sympathetic neuronal traffic from there is an associated feature of the hypotensive response (Schmitt & Fénard, 1970). The baroreceptor reflex component of the response to occlusion of the carotid arteries is inhibited by dihydroergotamine (Euler & Hesser, 1947), although in at least one report (Sutton, Cerletti & Taeschler, 1950), the effects are weak and only observed with doses which block α-adrenoceptors.

(c) *Peripheral vasoconstriction.* Even when systemic blood pressure falls after intravenous injection of dihydroergotamine in intact animals, there is evidence that some peripheral blood vessels (Rothlin, 1946/1947; Chu & Stürmer, 1973) including

those of the cerebral vascular bed (Carpi & Virno, 1957) are constricted. When the vasomotor centres in the medulla or the efferent sympathetic pathways are inactivated (by for instance pithing or ganglion blockade), even small doses of dihydroergotamine cause peripheral vasoconstriction and through this an increase in blood pressure (Konzett & Rothlin, 1953). Dihydroergotamine is some 10 to 25 times less potent than ergotamine as a peripheral vasoconstrictor agent in cats and dogs (Aellig, 1967; Owen & Stürmer, 1972), but shares with ergotamine a selective constrictor effect on the capacitance vessels of the perfused cat limb and a susceptibility to blockade by α-adrenoceptor antagonist drugs (Owen & Stürmer, 1972; Chu & Stürmer, 1973).

Significant vasoconstrictor activity is also seen with low concentrations of dihydroergotamine *in vitro* in the rabbit hind limb (Meier & others, 1957) and isolated segments of arteries (Carroll & others, 1972; Carroll & Glover, 1973) and veins (Müller-Schweinitzer, 1974b). Vasoconstriction was only partly antagonized by high concentrations of phentolamine (Müller-Schweinitzer, 1974b), and as with ergotamine, evidence has been obtained that enhanced prostaglandin synthesis and release is a contributory factor to the vasoconstrictor response produced (Müller-Schweinitzer, 1974b).

(d) *α-Adrenoceptor blockade.* Relative potency determinations show that dihydroergotamine is between 7 times (dog blood pressure, guinea-pig seminal vesicle) and 2 to 3 times (rabbit ear, hind limb, uterus, dog femoral vein) more potent than ergotamine in blocking responses to noradrenaline or adrenaline mediated by α-adrenoceptors (Rothlin, 1946; Gaddum & Hameed, 1954; Meier & others, 1957; Pacha & Salzmann, 1970). Significant inhibition of the cardiovascular responses to adrenaline and noradrenaline were seen in rats and cats with doses of dihydroergotamine within the therapeutic range (Rothlin, 1946; Outschoorn & Jacob, 1960) although in dogs, somewhat higher doses were required (Pacha & Salzmann, 1970). *In vitro*, the concentrations of dihydroergotamine producing 2-fold antagonism of noradrenaline responses on rabbit aorta, auricular artery and duodenum and dog femoral and saphenous veins fell within the range 0·3 to 6 ng ml^{-1} (Furchgott, 1955; Fozard, 1973; Müller-Schweinitzer, 1974a) which indicates the consistently high potency of dihydroergotamine as an antagonist of α-adrenoceptors in a variety of tissues.

α-Adrenoceptors are also suggested to be present on or near terminal sympathetic fibres which, when activated, mediate feed-back inhibition of the stimulation evoked secretion of noradrenaline (Starke, 1972; Starke & Altmann, 1973). Antagonists of these receptors increase transmitter overflow by interrupting the feedback cycle (Starke, 1972). Dihydroergotamine increased the release of noradrenaline evoked by stimulation of the sympathetic nerves to the cat spleen (Salzmann & others, 1968) and rabbit heart (Starke, 1972) in concentrations between 50 and 190 ng ml^{-1}. An explanation other than blockade of transmitter re-uptake must be considered for this effect since dihydroergotamine had no inhibitory action on the uptake of exogenous noradrenaline in concentrations up to 6 μg ml^{-1} (Starke, 1972). By analogy with the effects produced by low concentrations of other α-adrenoceptor antagonist drugs, interruption of the inhibitory feed-back cycle as suggested by Starke (1972) is the logical alternative explanation.

(e) *Blockade of 5-hydroxytryptamine vasoconstriction.* Dihydroergotamine, like ergotamine, is a potent antagonist of the blood pressure rise produced by 5-hydroxytryptamine *in vivo* (Hotovy & Roesch, 1958; Outschoorn & Jacob, 1960) and the

vasoconstrictor responses of isolated rabbit ears (Gaddum & Hameed, 1954) hind limbs (Meier & others, 1957) aorta (Innes, 1962b) and auricular artery (Carroll & others, 1972; Fozard, 1973). Also like ergotamine, the antagonism is selective in that the stimulant effects of 5-hydroxytryptamine on extra-vascular smooth muscle are little affected even by high concentrations of dihydroergotamine (Gaddum & Hameed, 1954; Bhattacharya, 1955; Salzmann & Kalberer, 1973).

(ii) *High dose/concentration effects*

Little remains for this section, except to record that dihydroergotamine is some 6 to 10 times less potent than ergotamine in blocking 5-hydroxytryptamine uptake into the perfused spleen (Salzmann & Kalberer, 1973) or blood platelets (Lingjaerde, 1970).

Clinical relevance

In view of the pharmacological similarity between dihydroergotamine and ergotamine, it would be illogical to assume that any property other than peripheral vasoconstriction was clinically important in the acute attack. However, dihydroergotamine also has value in the prophylaxis of migraine and here, since we know relatively little about how attacks are initiated or the preheadache phase in general, the choice of a therapeutically relevant property is more difficult. Faced with such a multiplicity of actions, comparison with other prophylactic agents is justified. It may be significant that at clinical dose levels dihydroergotamine shares with methysergide (section 2A) and clonidine (section 2B) only the property of peripheral vasoconstriction.

C. CAFFEINE

In practice, caffeine is only given in conjunction with ergotamine and its overall value in migraine has recently been questioned because of its central stimulating properties (Wilkinson, 1971). Nevertheless, it does significantly improve the clinical effectiveness of ergotamine tartrate given enterally. From the work of Berde, Cerletti & others (1970), there seems a strong possibility that enhanced intestinal absorption of ergotamine by caffeine is the primary mechanism by which this is brought about. However, another possible explanation comes from the observation that caffeine increases cerebral vascular resistance although it is weakly vasodilator elsewhere in the body (Ritchie, 1970). One mechanism by which vasoconstriction may be produced has been investigated in animal tissues. Methyl xanthines, including caffeine, enhance the constrictor responses of vascular smooth muscle to catecholamines (Bartelstone, Nasmyth & Telford, 1967; Kalsner, 1971) probably by inhibiting their inactivation by catechol *O*-methyl transferase. This specific action of prolonging the effects of the sympathetic transmitter substances might not only provoke localized vasoconstriction, but also reinforce the vasoconstrictor effects of ergotamine which are believed to be clinically important.

D. ASPIRIN AND PARACETAMOL

Probably more patients with migraine are helped by the simple analgesics aspirin and paracetamol than by any other type of therapy (Wilkinson, 1971). Until recently the mechanism of action of aspirin-like drugs was unknown, although it was generally considered that they produced their effects by interfering locally in the tissues with

some stage in the humoral mediation of the body's defensive reaction (Collier, James & Schneider, 1966; Collier 1969). One of the principal observations, that aspirin-like drugs antagonized the peripheral effects of bradykinin (Collier & others, 1966; Collier, 1969), was especially relevant to migraine, since Wolff and his colleagues had demonstrated the accumulation of kinin hormones in the blood vessel walls and perivascular tissue during a migraine attack (Dalessio, 1972). It was problematical however that kinin blockade by aspirin-like drugs was highly capricious with respect to the site, species and circumstances of the test (Collier, 1971).

The first clue that the bradykinin inhibitory responses of the aspirin-like drugs might result from interference with the generation of a second humoral mediator was provided by Piper & Vane (1969). They showed that bradykinin liberated rabbit aorta contracting substance from guinea-pig lung and that aspirin-like drugs blocked the release process. Rabbit aorta contracting substance is now thought to be the cyclic endoperoxide precursor of the prostaglandins (Hamburg & Samuelsson, 1973) and the subsequent work of Vane and his colleagues (see review by Ferreira & Vane, 1974) has established beyond doubt that aspirin and paracetamol inhibit the synthesis of prostaglandins in a wide variety of tissues in concentrations below those found in the plasma after therapeutic doses.

Although the relevance of prostaglandins to migraine is not established, a strong case for a putative role can be advanced on theoretical grounds. Thus, they are readily synthesized and released from most body tissues in response to stimuli varying from physiological to pathological (Piper, 1973). In minute concentrations they cause vasodilation, an increase in small vessel permeability, sensitization of pain receptors to nociceptive stimuli and inhibition of autonomic neuronal transmitter release (for references, see Brody, 1973; Cuthbert, 1973; Ferreira & Vane, 1974). Further, they cause headaches, described as migraine-like, when infused intravenously in humans (Carlson, Ekelund & Orö, 1968). Finally, a pharmacologically active lipid has been detected in the cerebrospinal fluid of patients during a migraine attack, which was absent during the attack-free period (Barrie & Jowett, 1967).

An additional, potentially relevant, observation is that prostaglandins can be released from isolated rat, guinea-pig or dog lung by 5-hydroxytryptamine perfused into the pulmonary artery at concentrations between 50 and 1000 ng ml^{-1} (Alabaster & Bakhle, 1970). This 5-hydroxytryptamine-induced release of spasmogens can be abolished non-selectively by aspirin-like drugs (Alabaster, 1971; Bakhle & Smith, 1972) and selectively by methysergide (Bakhle & Smith, 1974a; section 2A below). Although the concentration of 5-hydroxytryptamine found free in the plasma of normal humans is less than this at between 2 and 45 ng ml^{-1} (Crawford, 1963), even a small increase may be sufficient to induce spasmogen release from the lungs (or other tissues—see section 2A below) of susceptible individuals and initiate a migraine attack (Sandler, 1972).

Clearly, the potential relevance of the actions of aspirin and paracetamol in migraine extends to more than simple analgesia. It is probably true that if discovery of the effects of these compounds on prostaglandin synthesis had preceded knowledge of their therapeutic effectiveness, we should have concluded that prostaglandins were fundamentally important in the aetiology of migraine. Such a conclusion is certainly not invalidated by any of the established biochemical or pathophysiological features of migraine. It is strengthened by the observation that the most effective prophylactic drug we have available, methysergide, inhibits 5-hydroxytryptamine-evoked pulmonary spasmogen release in minute concentrations (Section 2A).

2. DRUGS USED PROPHYLACTICALLY

A. METHYSERGIDE

(i) *Low dose/concentration effects*

The minimum dose of methysergide which produces a pharmacological response *in vivo* is about 2 μg kg^{-1}. If the equivalent of the daily therapeutic dose (29 to 86 μg kg^{-1}) is given in acute experiments, one can observe antagonism of 5-hydroxytryptamine pharmacological responses and peripheral vasoconstriction.

(a) *Antagonism of 5-hydroxytryptamine.* Methysergide blocks a wide variety of responses to 5-hydroxytryptamine both *in vivo* and *in vitro*. Doses between 2 and 70 μg kg^{-1} injected subcutaneously inhibit oedema induced by 5-hydroxytryptamine in the hind paws of anaesthetized rats (Fanchamps, Doepfner & others, 1960), and the effect is selective since methysergide has no effect on oedema induced by histamine (Jori, Bentivoglio & Garattini, 1961). Aspirin-like drugs are also effective inhibitors of oedema and inflammation induced by 5-hydroxytryptamine (Keleman, 1957; Theobald & Domenjoz, 1958; Van Cauwenberge, Lapière & others, 1959), which implies an intermediary role for prostaglandins in the production of the response.

A slightly higher subcutaneous dose (80 μg kg^{-1}) abolished the stimulant effects of 5-hydroxytryptamine on the rat uterus (Fanchamps & others, 1960). By the intravenous route, the pressor effects of 5-hydroxytryptamine in dogs (Fanchamps & others, 1960) and pithed rats (Fozard & Leach, 1968) were abolished by low doses of methysergide (10 to 40 μg kg^{-1}). Recent work has disclosed an unusual situation with respect to the blockade of 5-hydroxytryptamine vasoconstrictor responses in specific vascular beds. Thus, although 5-hydroxytryptamine responses in the kidney and leg vasculature were strongly inhibited by 5 to 10 μg kg^{-1} of methysergide (Fanchamps & others, 1960), those in the nose (Vargaftig & Lefort, 1974) and the carotid artery bed (Saxena, 1972) were resistant to doses of methysergide as high as 500 to 640 μg kg^{-1} injected intravenously.

A very similar situation exists *in vitro*. Concentrations of methysergide between 0·1 and 5 ng ml^{-1} inhibited the responses to 5-hydroxytryptamine on a variety of smooth muscle preparations from the gastrointestinal tract (Bartlett & Hassan, 1968; Görlitz & Frey, 1973; Bakhle & Smith, 1974a) and uterus (Fanchamps & others, 1960) and less than 100 ng ml^{-1} strongly inhibited the effects on bovine pulmonary vein (Eyre, 1971). In contrast, responses of the isolated rabbit auricular artery (a branch of the carotid artery) to 5-hydroxytryptamine were unaffected by methysergide at a concentration of 20 ng ml^{-1} and were actually significantly enhanced during perfusion with 200 ng ml^{-1}. At this concentration methysergide itself produced vasoconstriction (Fozard, 1973). The immunity of 5-hydroxytryptamine-evoked carotid artery vasoconstriction to blockade by other classical D receptor antagonists has been repeatedly observed (Saxena & others, 1971; Saxena, 1972; Fozard, 1973).

The lung is potentially the most important site where antagonism of 5-hydroxytryptamine by methysergide has been demonstrated. 5-Hydroxytryptamine perfused through isolated rat, guinea-pig or dog lungs at concentrations between 50 and 1000 ng ml^{-1} induces the release of spasmogens, mainly prostaglandins, into the perfusion fluid (Alabaster & Bakhle, 1970). Methysergide in the extremely low concentration of 1·8 ng ml^{-1} abolished spasmogen release and in the presence of this concentration of methysergide, the threshold dose of 5-hydroxytryptamine to effect release was increased more than 5-fold (Bakhle & Smith, 1974a).

(b) *Peripheral vasoconstriction.* Intravenous administration of 20 to 80 μg kg^{-1} of methysergide to anaesthetized dogs and cats and pithed rats resulted in minimal effects on blood pressure (Fanchamps & others, 1960; Fozard & Leach, 1968; Saxena, 1974), and there was little change in the resistance to flow through the vascular beds supplied by the femoral, renal, superior mesenteric and vertebral arteries (Fanchamps & others, 1960; Saxena, 1974). In marked contrast, however, there was a dose related decrease in blood flow and peripheral resistance in the internal and external carotid artery beds of dogs (Saxena, 1974) and a fall in cephalic venous pressure (Cerletti & others, 1960). The discussion of ergotamine (section 1A) lists several reasons for the selectivity of this drug's action on the carotid artery bed and similar reasons could be advanced to explain the selectivity observed with methysergide.

A small dose of methysergide in the spinal cat (20 μg kg^{-1}) or larger doses in anaesthetized dogs (80 to 640 μg ml^{-1}) produced small but significant increases in blood pressure (Fanchamps & others, 1960; Saxena, 1974) accompanied by an increase in peripheral resistance mainly in the vasculature supplied by the carotid artery (Saxena, 1974; Vargaftig & Lefort, 1974). Confirmation of these *in vivo* vasoconstrictor actions has been obtained *in vitro* where concentrations of methysergide between 20 and 200 ng ml^{-1} contracted the isolated bovine pulmonary vein (Eyre, 1971) and the rabbit auricular artery (Carroll & Glover, 1973; Fozard, 1973). Constriction was not the result of activation of α-adrenoceptors since it was unaffected by concentrations of phentolamine which abolished responses to noradrenaline (Fozard, 1973). It was however abolished by perfusion with 10 ng ml^{-1} of the 5-hydroxytryptamine D receptor antagonist drugs cyproheptadine and pizotifen (Carroll & Glover, 1973).

(ii) *Medium dose/concentration effects.*

I include in this section sensitization of smooth muscle and inhibition of vasomotor reflexes.

(a) *Sensitization of smooth muscle.* Intravenous infusion of methysergide into anaesthetized cats at the rate of 17 μg kg^{-1} min^{-1} enhanced the contractile response of the nictitating membrane to noradrenaline and sympathetic nerve stimulation and the blood pressure response to noradrenaline (Dalessio, Camp & others, 1962). Similarly in the dog, methysergide caused a maximum 2-fold enhancement of the vasoconstrictor responses to noradrenaline in the carotid artery bed at a dose of 80 μg kg^{-1} (Saxena, 1972). Sensitization is unlikely to result from depression of cardiovascular reflexes (see below) since only with intravenous doses higher than 160 μg kg^{-1} is depression obtained (Cerletti & others, 1960; Saxena, 1974). Further, significant vascular sensitization to both nerve stimulation and vasoconstrictor drugs has been observed on the rabbit auricular artery *in vitro* (Fozard, 1973) where reflex effects are absent. Since methysergide affects monoamine tissue uptake only at high concentrations (Salzmann & Kalberer, 1973), the explanation may well be that methysergide produces subthreshold stimulation which achieves threshold or greater levels in the presence of other stimulant procedures.

(b) *Inhibition of baroreceptor vasomotor reflexes.* Predictably, since methysergide is an ergot derivative, the reflex rise in blood pressure resulting from occlusion of the carotid arteries is abolished dose-dependently in both dogs (Saxena, 1974) and cats (Cerletti & others, 1960; Dalessio & others, 1962). Intravenous infusions between 5

and 25 μg kg^{-1} min^{-1} or single injections of 160 to 640 μg kg^{-1} were required and the effect was selective in that depressor responses to afferent stimulation of the vagus were unaffected (Dalessio & others, 1962).

(iii) *High dose/concentration effects*

In vivo, doses of methysergide in excess of 5 mg kg^{-1} produced a non-specific anti-inflammatory action in rats (Dalessio & others, 1962) and protected rat platelets against loss of their 5-hydroxytryptamine induced by injection of reserpine (Owen & others, 1971). *In vitro*, concentrations of methysergide between 1 and 3 μg ml^{-1} were required to inhibit 5-hydroxytryptamine-evoked platelet aggregation (Cumings & Hilton, 1971) and the uptake of 5-hydroxytryptamine by the spleen (Salzmann & Kalberer, 1973). In contrast to the latter observation, the uptake of 5-hydroxytryptamine by the rabbit heart was unaffected by methysergide (1 μg ml^{-1}) (Fozard & Berry, 1974).

Clinical relevance

Methysergide is used only as a prophylactic agent and has no beneficial effects once the attack has started. As mentioned earlier under dihydroergotamine the important therapeutic property in a prophylactic drug may not necessarily be directed towards antagonism of the extra-cranial vasodilation of the headache phase, but more towards inhibition of the mechanisms responsible for initiating and maintaining the attack. Because these factors are unknown, one has little justification for choosing any particular property as being of clinical importance. However, certain priorities are suggested by observations from animal experiments.

Thus, the clear demonstration that carotid arterial vasoconstriction evoked by 5-hydroxytryptamine is resistant to blockade by methysergide would suggest a minor role if any for antagonism of 5-hydroxytryptamine vasoconstrictor responses in the clinical situation. Such a view has been repeatedly advanced in recent years (Lance, Anthony & Hinterberger, 1970; Saxena & others, 1971; Fozard, 1973; Saxena, 1974), and even Sicuteri, who introduced methysergide into therapy on the basis of its 5-hydroxytryptamine antagonist properties, has recently suggested that mimicking rather than antagonizing 5-hydroxytryptamine may be its important clinical action (Fanciullacci, Franchi, & others, 1974).

The most potent and potentially most clinically relevant pharmacological property of methysergide is the selective inhibition of the inflammatory response evoked by subdermal injection of 5-hydroxytryptamine. Experiments with aspirin-like drugs indicate that the inflammatory response is mediated, at least in part, by a local release of prostaglandins, and it seems likely that methysergide is interfering with this release. Thus, a release of spasmogens including prostaglandins has been clearly demonstrated in isolated perfused lungs, and in this test system, methysergide is a powerful and specific inhibitor of the release evoked by tryptamine and 5-hydroxytryptamine.

The selective suppression by methysergide of the release of pro-inflammatory substances can be considered a clinically relevant property: firstly, because as discussed in section 1D above, prostaglandins may be concerned in the initiation and maintenance of a migraine attack; secondly, because the effects are produced at doses and concentrations likely to be achieved in the clinical situation. The selectivity of action of methysergide would also implicate 5-hydroxytryptamine as the most likely stimulus

to spasmogen release, which adds further significance to the changes in blood 5-hydroxytryptamine concentrations which are known to accompany a migraine attack (Curran & others, 1965; Anthony & others, 1967; final section below).

Finally, the circulatory effects of methysergide must be considered. Although vasomotor reflex inhibition cannot be ruled out entirely as a factor in the antimigraine action, it is manifested only at much higher doses than are needed to constrict the vessels of the carotid artery bed. Direct vasoconstriction, reinforced perhaps by sensitization of the peripheral vasculature to sympathetic stimulation and vasoconstrictor drugs, could raise the threshold for initiation of the unrestrained extracranial vasodilation which is a characteristic feature of migraine headache.

In conclusion therefore, a combination of selective suppression of tissue spasmogen release and direct vasoconstriction, supplemented perhaps by vascular sensitization, seem most likely to explain the undoubted clinical effectiveness of methysergide.

B. CLONIDINE

(i) *Low dose/concentration effects*

A measure of the difficulty in relating the animal pharmacology of clonidine to its therapeutic effect can be inferred from the fact that the usual daily prophylactic dose (1 to 2 μg kg^{-1}) is some 2 to 3 times less than the minimum dose which when injected intravenously produces a pharmacological response in animals. Clonidine is, however, somewhat exceptional in that it was introduced as a potential antimigraine drug on the basis of the results from animal experiments designed to mimic the conditions of prophylactic drug treatment (Zaimis & Hanington, 1969). These authors gave clonidine daily by mouth to cats in doses of 10 to 20 μg kg^{-1} and estimated the changes in hind limb vascular reactivity after 1 or 4 weeks. There was a decreased sensitivity to adrenaline, noradrenaline, isoprenaline and angiotensin which, it was suggested, would be a desirable property for a potential antimigraine drug. Regrettably, chronic experiments of this sort are the exception rather than the rule, and the rest of this section has little option but to concern itself with the effects produced after acute administration of clonidine.

The threshold dose for producing pharmacological effects *in vivo* is about 2 μg kg^{-1} and with doses up to 10 μg kg^{-1} three properties have been described. These are an effect on the central nervous system to alter the outflow of sympathetic and vagal tone, a peripheral vasoconstrictor action and the senstitization of vascular smooth muscle to stimulant drugs.

(a) *Alteration of central sympathetic and vagal tone.* In cats, dogs, monkeys, rabbits and rats intravenous injection of clonidine between 2 and 10 μg kg^{-1} produces a short-acting pressor response of 1 to 2 min duration which is superceded by a sustained depressor response accompanied by bradycardia which may last up to 2 h (Boissier, Giudicelli & others, 1968; Constantine & McShane, 1968; Nayler, Price & others, 1968; Rand & Wilson, 1968; Bolme & Fuxe, 1971). The brief rise in blood pressure is the result of peripheral vasoconstriction and is discussed in section (b) below. The hypotensive phase results mainly from a decrease in cardiac output (Kobinger & Walland, 1967; Naylor & others, 1968) which arises from a combination of bradycardia and a reduction in cardiac performance (Laubie & Schmitt, 1974) and systemic venodilation (Naylor & others, 1968). A reduction in peripheral resistance may also

contribute especially after low doses (Ng, Phelan & others, 1967; Constantine & McShane, 1968), although prominent hypotension has been observed with no change (Kobinger & Walland, 1967; Autret, Schmitt & others, 1971) or even an increase (Laubie & Schmitt, 1969; Kobinger, 1970) in the total peripheral resistance.

There is sound evidence that hypotension and bradycardia result from an action of clonidine on the central nervous system and in particular the medulla oblongata. Thus, injection of small doses directly into this region (Kobinger & Walland, 1967) or the vertebral artery (Sattler & Van Zwieten, 1967; Constantine & McShane, 1968; Katic, Lavery & Lowe, 1972) produces hypotensive effects comparable to much larger doses injected intravenously. The central action of clondine results in a decrease in nervous impulse flow in postganglionic sympathetic fibres (Schmitt, Schmitt & others, 1967; Klupp, Knappen & others, 1970; Woodhouse, Ram & Garvey, 1972) and an increase in the impulse traffic in the vagus (Woodhouse & others, 1972) the latter probably as a result of enhancement of pressure sensitive compensatory reflex activity (Robson, Kaplan & Laforce, 1969; Kobinger & Walland, 1972a,b). The relative importance of inhibition of the sympathetic or enhancement of the vagal outflows to the production of hypotension varies widely depending on the conditions of the experiment. Thus, in the dog, each factor contributed significantly to the cardiac slowing and impaired cardiac performance (Constantine & McShane, 1968; Laubie & Schmitt, 1974). In the cat, on the other hand, hypotension and bradycardia seem to be entirely the result of withdrawal of sympathetic tone (Bentley & Li, 1968; Constantine & McShane, 1968; Rand & Wilson, 1968; Day & Roach, 1974).

Each of the central actions of clonidine has been shown to be absent after administration of recognized α-adrenoceptor blocking agents (Schmitt, Schmitt & Fénard, 1971; Bolme & Fuxe, 1971; Katic & others, 1972; Kobinger & Walland, 1972a, b; Day & Roach, 1974), which reinforces a mass of circumstantial evidence (Schmitt, 1970; Van Zwieten, 1973) that clonidine acts on α-adrenoceptors in the medulla. However, as has already been touched on briefly (section 1A) differences exist between the peripheral and central receptor sites with respect to the order of potencies of agonist drugs (Autret & others, 1971; Schmitt & Fénard, 1971) and their susceptibility to antagonist blockade (Schmitt & Schmitt, 1970; Katic & others, 1972). Although distributional factors will contribute to these differences (Van Zwieten, 1973), there may also be fundamental differences in the nature of the two receptor sites. In support of this contention, a recent series of papers has demonstrated the existence of specific adrenaline neurons in rat brain (Hökfelt, Fuxe & others, 1973, 1974) which appear to be involved in vasomotor control (Bolme, Corrodi & others, 1974). Low doses of clonidine are suggested to alter central vasomotor outflow in this species by activating specific adrenaline receptors which fit neither an α nor β classification (Bolme & others, 1974).

It is of interest at this stage to record that β-adrenoceptors are also suggested to be present in the central nervous system and to play a role in the control of central vasomotor outflow (for references, see Day & Roach, 1974). This may have relevance to migraine, since, propranolol, a non-selective β-adrenoceptor antagonist, has recently been proved to be of value in prophylactic treatment (Widerøe & Vigander, 1974). Although the mechanism of action of propranolol in migraine is unknown, it seems not to be a property common to all β-adrenoceptor antagonists. Thus, pindolol, a selective antagonist at β_1-adrenoceptors, displays no protective effects in migraine (Ekbom & Lundberg, 1972; Sjaastad & Stensrud, 1972).

(b) *Peripheral vasoconstriction.* The hypotensive response to low doses of clonidine is abolished in all species by mechanical or pharmacological interruption of the efferent nerve supply, and under these conditions clonidine evokes a sustained rise in blood pressure accompanied by an increase in total peripheral resistance (Bentley & Li, 1968; Constantine & McShane, 1968; Nayler & others, 1968; Rand & Wilson, 1968). The fact that vasoconstriction is normally present at low doses but is masked by the centrally mediated hypotensive component would explain why hypotension often occurs without a fall in total peripheral resistance (Laubie & Schmitt, 1969; Kobinger, 1970; Autret & others, 1971). Significantly, from the point of view of migraine perhaps, one of the areas in cats and dogs in which an increase in resistance occurs irrespective of the change in systemic blood pressure is the cerebral vascular bed (Laubie & Schmitt, 1969; Zaimis, 1970).

Peripheral vasoconstriction after clonidine is mediated by α-adrenoceptors, since it is selectively blocked by low concentrations of phentolamine and phenoxybenzamine (Nayler & others, 1968; Rand & Wilson, 1968). It is also direct since it persists in the presence of large doses of catecholamine uptake blocking agents (Rand & Wilson, 1968) or after sympathetic transmitter depletion by reserpine (Nayler & others, 1968). Confirmation of these *in vivo* findings has been obtained *in vitro*. Thus, the vessels of the rabbit ear and segments of the auricular artery constricted to concentrations of clonidine between 10 and 50 ng ml^{-1} (Boissier & others, 1968; Hodge & Robinson, 1972; Fozard, 1973), and although unaffected by reserpine (Fozard, 1973) or denervation (Hodge & Robinson, 1972) the responses were competitively antagonized by phentolamine to give a pA_2 value identical to that obtained when noradrenaline was used as the agonist (Fozard, 1973). Clonidine also constricts strips from rabbit aortae and dog popliteal veins and again activation of α-adrenoceptors is the operative mechanism (Constantine & McShane, 1968).

(c) *Sensitization of vascular smooth muscle.* Increased cardiovascular reactivity has been reported after intravenous injection of clonidine in intact cats, dogs and rats. Blood pressure responses to adrenaline, noradrenaline and the nicotinic receptor stimulant drug dimethylphenylpiperazinium (but not electrical stimulation of the vasomotor outflow—see below) were enhanced by doses of clonidine between 1 and 20 $\mu g\ kg^{-1}$ (Bentley & Li, 1968; Boissier & others, 1968; Rand & Wilson, 1968). The phenomenon can be explained in part by the inhibitory effect of clonidine on vasomotor outflow since sensitization was less in animals whose brain and spinal cord had been destroyed (Bentley & Li, 1968). There may also be a peripheral component however, since a generalized increase in sensitivity to vasoconstrictor drugs has been reported in the isolated auricular artery during perfusion with concentrations of clonidine as low as 2 ng ml^{-1} (Fozard, 1973).

(ii) *Medium dose/concentration effects*

I include in this section depression of cardiovascular reflex mechanisms and inhibition of peripheral sympathetic neuronal transmitter release.

(a) *Inhibition of cardiovascular reflexes.* The response to carotid occlusion is inhibited by clonidine in most species at intravenous dose levels between 10 and 50 $\mu g\ kg^{-1}$ (Boissier & others, 1968; Rand & Wilson, 1968). The site of action is unquestionably central (Sattler & Van Zwieten, 1967; Katic & others, 1972). Not all cardiovascular reflexes are inhibited to the same extent however, and although there are inconsisten-

cies between different workers (Sattler & Van Zwieten, 1967; Schmitt, 1970), chemoreceptor reflexes seem to be more resistant to blockade than reflexes elicited via baroreceptors (Schmitt, 1970). This probably explains why even the inhibitory effects on the carotid occlusion reflex are highly variable both between and, occasionally, within species (Boissier & others, 1968; Bentley & Li, 1968; Rand & Wilson, 1968).

(b) *Inhibition of peripheral sympathetic neuronal transmitter release.* Doses of clonidine between 10 and 30 μg kg^{-1} inhibited both the blood pressure (Boissier & others, 1968) and the heart rate (Armstrong & Boura, 1973) responses to submaximal stimulation of the entire sympathetic outflow in the pithed rat. This effect was suggested to result from a specific inhibition of noradrenaline release at the adrenergic nerve endings (Armstrong & Boura, 1973) for which there is sound *in vitro* evidence. In rabbit isolated hearts and rat irides clonidine (4–40 ng ml^{-1}) decreased transmitter release from peripheral adrenergic nerves in response to nerve impulses (Farnebo & Hamberger, 1971; Starke, Wagner & Schümann, 1972) by an action on neuronal α-adrenoceptors (Starke & Altmann, 1973).

(iii) *High dose/concentration effects*

Doses of clonidine between 100 and 750 μg kg^{-1} cause depression of the central nervous system manifested as sedation, an increase in hypnotic sleeping time, loss of righting reflex and significant inhibition of conditioned avoidance and rotarod performance (Ng, Phelan & others, 1967; Delbarre & Schmitt, 1971). Production of local anaesthesia (Starke & others, 1972), blockade of α-adrenoceptors (Bentley & Li, 1968; Ng & others, 1967; Hodge & Robinson, 1972; Fozard, 1973), inhibition of catecholamine uptake$_2$ (Salt, 1972) with no effects on uptake$_1$ (Salt, 1972; Starke & others, 1972) and a stimulant effect on cardiac histamine (H2) receptors (Csongrady & Kobinger, 1974) are just some of the other properties of clonidine which occur at doses and concentrations far in excess of therapeutic levels.

Clinical relevance

The original observation of Zaimis & Hanington (1969) that vascular reactivity in cats decreased after several days treatment with clonidine was the basis for the drug being introduced as a prophylactic agent in migraine. However, it should be emphasised that the daily dose of clonidine used in the experiments of Zaimis & Hanington was some 5 to 10 times greater than that found to be effective therapeutically. Further, recent chronic experiments in dogs have demonstrated no change in the cardiovascular reactivity after administration of 20 μg kg^{-1} of clonidine orally for seven days (Katic & others, 1972). The evidence is thus far from convincing that clonidine exerts its protective effects in migraine by depressing cardiovascular reactivity.

When the acute effects of clonidine at low and medium doses or concentrations are assessed as candidates for a therapeutic role, inhibition of baroreceptor reflexes can be discounted on the grounds that reflex activity remains intact at clinical dose levels (Zaimis, 1970). In practice, this leaves inhibition of spontaneous sympathetic outflow and direct vasoconstriction (reinforced perhaps by an increased peripheral vascular sensitivity) for consideration. For the reasons outlined above for dihydroergotamine and methysergide, either, neither or both these low dose properties could be important to the prophylactic mechanism of action. Faced with having to decide on just one clinically relevant property, prejudice would be appropriate towards

peripheral vasoconstriction since this is a property also seen with low doses of methysergide, the most effective prophylactic drug available.

C. CYPROHEPTADINE AND PIZOTIFEN

Cyproheptadine and pizotifen are discussed together and somewhat briefly for several reasons. Firstly, because they have a similar chemical structure and pharmacological profile, secondly, because both are significantly less effective than methysergide in the treatment of migraine (Lance, 1973), and finally, because with pizotifen in particular, few absolute quantitative data seem to be available.

(i) *Low dose/concentration effects*

Both cyproheptadine and pizotifen are more potent antagonists of the effects of histamine and 5-hydroxytryptamine than many specific antagonists of either compound, and only slightly less potent than atropine as antagonists of acetylcholine.

In acute experiments, doses of cyproheptadine and pizotifen well within the daily therapeutic range (Table 2) antagonized the effects of 5-hydroxytryptamine on the dog blood pressure, guinea-pig bronchioles and rat paw oedema test *in vivo* and on guinea-pig ileum, rat fundus, rat uterus and rabbit auricular artery *in vitro* (Stone, Wenger & others, 1961; Vargaftig, Coignet & others, 1971; Carroll & others, 1972; Speight & Avery, 1972; Carroll & Glover, 1973; Frankhuyzen & Bonta, 1974). Pizotifen (but not cyproheptadine) has also been tested for its ability to inhibit the prostaglandin release evoked by 5-hydroxytryptamine from the isolated perfused rat lung (Bakhle & Smith, 1974a). In contrast to methysergide, which suppressed prostaglandin release at a perfusion concentration of 1·8 ng ml^{-1}, pizotifen was only weakly effective, 300 ng ml^{-1} being the equivalent inhibitory concentration.

There is at least one response to 5-hydroxytryptamine which is demonstrably resistant to blockade by cyproheptadine even in doses up to 5 mg kg^{-1} injected intravenously, and that is vasoconstriction of the vessels supplied by the carotid artery (Saxena, 1972). In this respect, cyproheptadine behaves in a similar manner to methysergide (section 2A). Similarly, on an isolated extracranial artery from the rabbit, both cyproheptadine and pizotifen were only weak antagonists of the vasoconstrictor responses to 5-hydroxytryptamine. Further, the antagonism was non-specific since responses to potassium ion were similarly depressed (Fozard, unpublished).

Both cyproheptadine and pizotifen are particularly potent inhibitors of the effects of histamine on dog blood pressure, guinea-pig bronchioles and the rat paw oedema test *in vivo*, and guinea-pig ileum and rabbit auricular artery *in vitro* (Stone & others, 1961; Speight & Avery, 1972; Fozard, unpublished; Glover, personal communication).

The high potencies of cyproheptadine and pizotifen as antagonists of acetylcholine is evident from the fact that on guinea-pig ileum they were only between 2·5 and 5 times less potent than atropine respectively. On the rat fundus, cyproheptadine was some 4 times more potent as an antagonist of acetylcholine than as an antagonist of 5-hydroxytryptamine (Frankhuyzen & Bonta, 1974).

(ii) *Medium dose/concentration effects*

I include in this section the effects of cyproheptadine and pizotifen on the central nervous system although I acknowledge that rather large doses are required to elicit

some of the effects observed. Cyproheptadine at doses between 0·2 and 5 mg kg^{-1} produces a diffuse depression of the central nervous system manifested as sedation, inhibition of both spontaneous and amphetamine-evoked motor activity in mice, block of acoustic arousal in rats and rabbits and prolongation of barbiturate sleeping time (Vargaftig & others, 1971; Van Riezen, 1972). Pizotifen had similar depressant activity in these tests, but in addition possessed antidepressant activity. Thus, it was more potent than either imipramine or amitriptyline in reversing reserpine hypothermia, one of the standard tests for antidepressant activity, (Speight & Avery, 1972; Van Riezen, 1972). The central nervous system is therefore one site at which these two drugs differ qualitatively. Whereas pizotifen has both depressant and antidepressant activity, cyproheptadine is exclusively depressant.

(iii) *High dose/concentration effects*

At doses and concentrations of little clinical relevance, cyproheptadine and pizotifen reduce the responsiveness of various tissues to noradrenaline and bradykinin (Stone & others, 1961; Speight & Avery, 1972) and inhibit the uptake of 5-hydroxytryptamine by several tissues (Pfeiffer, Sadovsky & others, 1971; Salzmann & Kalberer, 1973). Cyproheptadine and pizotifen neither constricted peripheral blood vessels nor sensitized them to vasoconstrictor procedures (Stone & others, 1961; Carroll & others, 1972; Speight & Avery, 1972; Carroll & Glover, 1973; Fozard, unpublished).

Clinical relevance

The antagonism of the effects of histamine and acetylcholine exhibited by these compounds at low doses is unlikely to explain their clinical efficacy since neither the classical antihistamines nor the anti-acetylcholine drugs have been found to be especially useful in migraine. Antagonism of 5-hydroxytryptamine responses is a more probable explanation, although, as with methysergide, it is problematical that the vasoconstrictor effects of 5-hydroxytryptamine on the carotid artery bed were little affected even at high dose levels. Antagonism of the pulmonary prostaglandin release evoked by 5-hydroxytryptamine has not yet been tested for cyproheptadine, and pizotifen was over 150 times less potent than methysergide in this respect. Nevertheless, following the discussion of the potential importance of this property in sections 1D and 2A, an action at this site, however weak, may well be therapeutically relevant.

Comparison of the properties of cyproheptadine and pizotifen with methysergide and clonidine is rather unhelpful. They have little in common with clonidine, and share with methysergide only the antagonism of some 5-hydroxytryptamine responses. Of particular interest is the fact that neither cyproheptadine nor pizotifen have the direct and indirect effects on the peripheral circulation which are characteristic of both methysergide and clonidine at low dose levels.

The effects of cyproheptadine and pizotifen on the central nervous system which have been observed during therapy (Dalessio, 1972; Speight & Avery, 1972) seem most likely to be clinically important. Drugs with effects primarily on the central nervous system are of proven efficacy in migraine (Table 1), and both sedative and antidepressant properties seem to be of value. Cyproheptadine, through its sedative properties, and pizotifen with its combined sedative and antidepressant properties, may be beneficial in migraine by removing the secondary stress symptoms known to be associated with the condition (Dalessio, 1972).

Final comments

Consideration of the pharmacological actions of the antimigraine drugs as a whole indicates that no single property can be unequivocally correlated with clinical effectiveness. However, two effects merit brief further discussion. These are vasoconstriction and prostaglandin release evoked by 5-hydroxytryptamine.

I choose vasoconstriction because there can be little doubt of its relevance to the therapy of migraine. Thus ergotamine (and dihydroergotamine) almost certainly act in the acute attack by constricting dilated extracranial blood vessels. Similarly, the vasoconstrictor actions of the prophylactic drugs methysergide and clonidine, which are evident at the lowest doses used, must make conditions for extracranial vasodilation less favourable, and in this way lessen the severity of, and possibly retard the development of, the individual attacks.

The discovery of the prostaglandins and the evidence of their role in a number of pathological conditions has been one of the most exciting of recent developments in our understanding of disease processes. This area surely offers the best prospect for future research effort in migraine. Sandler has already hypothesized that migraine may be triggered by a release of pulmonary spasmogens, including prostaglandins, induced by changes in the plasma concentrations of certain biogenic amines (Sandler, 1972). Because of their relevance to dietary migraine, particular emphasis was placed on tyramine (Sandler, 1972) and phenylethylamine (Sandler, Youdim & Hanington, 1974). However, it may be 5-hydroxytryptamine, a particularly active stimulant of pulmonary spasmogen release (section 1D) *and* a normal constituent of human blood, which proves to be the important trigger factor in migraine in general.

In spontaneous migraine, whole blood 5-hydroxytryptamine concentrations fall by about 40% at the onset of the acute attack (Curran & others, 1965; Anthony & others, 1967). If, as seems likely (Saxena, 1970), there is an initial release of unmetabolized 5-hydroxytryptamine from the platelets, then not only would there be an associated increase in the "free" or physiologically active amine concentration (section 1D; Crawford, 1963), but the increase might well exceed the threshold for tissue spasmogen release, and as a result trigger a migraine attack. Similar reasoning would also apply to migraine attacks provoked by injections of reserpine (Kimball & others, 1960; Curzon, Barrie & Wilkinson, 1970; Carroll & Hilton, 1973), which are characteristically associated with a sharp fall in whole blood 5-hydroxytryptamine concentrations (Carroll & Hilton, 1973). The recent observation (Sandler & others, 1974), that platelets from migraine patients have a defective capacity to deaminate 5-hydroxytryptamine compared to normal controls, may be significant to both the above situations. Thus, a deficit in platelet monoamine oxidase would almost certainly mean more 5-hydroxytryptamine being released in the unmetabolized form during the initial stages of either a spontaneous or a reserpine induced attack.

To specify the lungs as the source of the amine-evoked spasmogen release would seem to be too restrictive. The results from animal experiments (section 2A) indicate that 5-hydroxytryptamine can release prostaglandins from tissues other than the lungs and produce peripheral inflammation as a result. Such an effect has also been demonstrated in humans where small doses of 5-hydroxytryptamine produced symptoms of inflammation when injected intradermally (Reid, 1952; Scherbel & Harrison, 1959), and headache after injection around the superficial temporal artery (Ostfield, 1960). Further, blood prostaglandin concentrations, which might be expected to increase if pulmonary prostaglandins were being released, were little altered during attacks of

migraine (Bennett, Magnaes & others, 1974; Anthony, 1974). It therefore seems possible that, in addition to the lung, a release of pro-inflammatory substances could occur in or near the tissues concerned in migraine.

Such theories are further supported by the fact that prostaglandins are now established as mediators of acute inflammation in man (Ferreira & Vane, 1974), that inhibitors of prostaglandin synthesis are effective in migraine therapy (section 1D) and that methysergide in minute doses and concentrations selectively inhibits prostaglandin release evoked by 5-hydroxytryptamine (section 2A). They have the additional advantage that they can be tested experimentally in both the clinical and non-clinical situation. Until proof or disproof is forthcoming, however, there are surely sound experimental reasons from animal work for combining therapy with prostaglandin synthesis inhibitors and methysergide. Sequential blockade of prostaglandin generation in this way might well bestow protection in migraine at relatively low doses of the constituent drugs and with consequently fewer side effects.

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