SEROTONIN ANTAGONISTS

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THE NATURE OF SEROTONIN

(1) General

It has been known to physiologists for at least a century that a vasoconstrictor material appears in serum when blood is allowed to clot, whilst a smooth muscle constrictor was isolated from the gut by Erspamer as early as 1937.[1] However, it was not until 1948 that the material was identified as 5-hydroxytryptamine (5HT) and named serotonin.[2] And yet serotonin remained a biochemical "orphan", a substance in search of a disease, until Lembeck[3] demonstrated that it was present in large amounts in carcinoid tumours. In fact, our knowledge concerning pathways of indole metabolism owes much to patients with this disease. Only since then has it been realised that serotonin has a bewildering array of physiological effects in the body.

Serotonin was propelled into further pharmacological prominence when it was discovered to be present in brain, and to be structurally related to lysergic acid diethylamide (LSD), a substance with spectacular psychotropic effects. Moreover its brain content was lowered by the tranquilising drug reserpine, thus suggesting that it can serve as a neurotransmitter, a function now established, which focused attention on a possible role of 5HT in mental illness.[4]

(2) Chemistry

Structurally serotonin is an amine which has the chemical name of 5-hydroxyindole-3-ethylamine, and a molecular weight of 176.2.[2] As it does not possess an asymmetric carbon atom it is optically inactive. It is usually found as the double salt with creatinine and is most stable in that combination.[2] The indole nucleus shows a characteristic fluorescence at 300 μm when activated at 280-290 μm at pH 3-10. Only 5-hydroxylated indoles exhibit a shift in the fluorescence band to 540 μm when the pH is lowered to 2 or less. This shift is characteristic and is used for the identification and estimation of 5HT and its derivatives.[5] Serotonin is formed in the body from the essential amino acid tryptophan. The metabolic pathway involved in its synthesis and breakdown is shown in Figure 1.

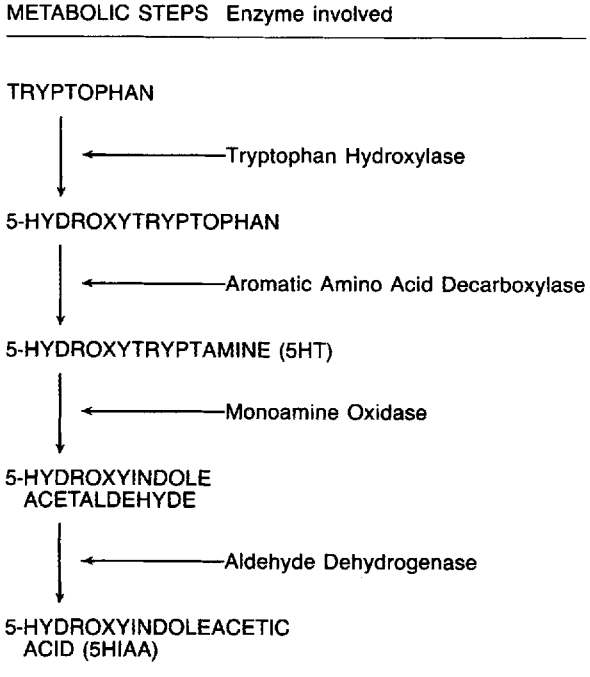

Figure 1: Biosynthesis and metabolism of serotonin (5-hydroxytryptamine, 5HT)

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TABLE 1
Physiological Effects of 5HT[41]

System	Function/Structure Affected	Usual Effect	Probable Mechanism
Cardiovascular	Blood pressure	Biphasic	? Pre-existing neurogenic tone
	Large arterioles/veins	Constriction	Smooth muscle contraction
	Arterioles capillaries	Dilatation	Smooth muscle relaxation
Gastrointestinal	Small intestine	Increase motility	Sensitisation of nucosal stretch receptors
	Stomach/colon	Inhibition	Sensitisation of nucosal stretch receptors
	Gastric juice	Stimulates secretion	? mechanism
Renal	Ureters	Contraction	Stimulation of ureteric smooth muscle
	Renal vessels	Constriction	Stimulation of vascular smooth muscle
Respiratory	Respiratory rate	Hyperventilation	Stimulation of carotid and aortic chemoreceptors
	Bronchial smooth muscle	Contraction	Stimulation of bronchial smooth muscle
	Pulmonary vessels	Contraction	Stimulation of vascular smooth muscle
Nervous	Peripheral nerve endings	Pain	Stimulation
	Pain perception	Increased	Decrease in brainstem 5HT
		Decreased	Increase in brainstem 5HT
Platelets	Aggregation	Aggregation without release reaction	Activation of specific receptors

(3) Physiology

The human body contains about 10 mg of 5HT, and 90% is found in the enterochromaffin cells of the gastrointestinal tract. Of the remainder, most of it is found in the blood (about 98% in platelets), and the central nervous system.[4] Serotenergic neurons are mostly contained in the raphe nuclei in the medulla, the pons, midbrain and centromedial reticular formation and have wide connections to the anterior and posterior horns of the spinal cord, the intermediolateral cell column, the ventral tegmentum, hypothalamus, amygdaloid nuclei, and the cingulate gyrus. In those sites serotonin serves as an inhibitory neurotransmitter.[6] In fact, projections from brainstem nuclei onto the neurones of the posterior horns of the spinal cord, are known to regulate transmission of pain impulses at that level. The pathways involved in this function are serotoninergic and their increased activity inhibits pain perception, whilst reduced activity leads to increased pain appreciation. Serotonin thus assumes an important role in nociception.

The action of 5HT on the various organs and body systems is through stimulation or inhibition of smooth muscle cells, peripheral sensory nerves and neurons of the CNS.

Responses to 5HT are variable. They differ according to the animal species, the animal type in the same species, and even in successive tests in the same individual. The variability is mainly due to:

1. reflex mediation of 5HT responses, which are influenced by a variety of factors, *e.g.* pattern of innervation, route and speed of injection, underlying muscle tone, and
2. the development of tachyphylaxis, where repetitive doses produce progressively smaller responses.

A brief outline of the major physiological effects of 5HT is given in Table 1.

SEROTONIN RECEPTORS

Identification and categorisation of 5HT receptors has been rather slow in contrast to those involved in the actions of catecholamines and histamine. In the past, two classes have been broadly recognised:

1. 5HT D-receptors, which mediate vasoconstriction and are blocked by D-lysergic acid diethylamide (LSD) and the currently available 5HT antagonists methysergide, pizotifen and cyproheptadine and, what is more surprising, by propranolol and to a lesser extent by amitriptyline, and
2. 5HT M-receptors, which mediate pain, are mostly located on terminal sympathetic fibres and afferent (sensory) nerves, and are blocked by morphine. They can also be blocked by metoclopramide as well as propranolol.[7]

Recently 5HT receptors have been reclassified using various agents labelled with tritium. Again two classes of receptors were identified:

1. $5HT_1$ receptors, labelled with [^{3}H]5HT. These are commonly blocked by methysergide, cyproheptadine and pizotifen and are found predominantly in the hippocampus, and
2. $5HT_2$ receptors, labelled with [^{3}H]spiperone, and blocked by ketanserin (a newer 5HT antagonist). In the brain such receptors are predominantly found in the frontal cortex.

They are also present on arterial and bronchial smooth muscle and are thought to be responsible for the contractile effects of serotonin (*e.g.* vaso- and broncho-constriction) and platelet aggregation, as well as the amplification of these processes by other agents, *e.g.* noradrenaline and angiotension II. Both $5HT_1$ and $5HT_2$ receptors will be labelled by [^{3}H]LSD. These receptors are different from D- and M- types, since morphine has no effect on them and phenoxybenzamine (another weak 5HT antagonist) has only a weak blocking action.[8]

Finally, two different receptor types have been identified in platelets, site A concerned with platelet aggregation responses and site B involved in uptake processes. The affinity of the two types of receptors for 5HT is such that a very high proportion of binding sites must be blocked by an inhibitor before aggregation is prevented.[9]

SEROTONIN ANTAGONISTS

There are several groups of drugs that affect endogenous 5HT but of those, serotonin antagonists (drugs which block the action of the amine at receptor sites) have proven to be most useful clinically.

Ergot alkaloids and related compounds were the earliest 5HT antagonists to be recognised and are active particularly on smooth muscle receptors. In the same group belong the lysergic acid derivatives, diethylamide (LSD) and methyl butanolamide (methysergide), which are particularly potent in this respect. A high order of 5HT antagonism is demonstrated by a host of other drugs, including tryptamine, histamine H_1 blockers of the ethylenediamine type (*e.g.* cyproheptadine) phenothiazines (*e.g.* chlorpromazine), halo-alkylamines (*e.g.* phenoxybenzamines) the various other adrenergic blocking agents.[10]

There is more than one mechanism involved in 5HT antagonism. Some drugs such as pizotifen and cyproheptadine, are classical competitive 5HT inhibitors, in that they block 5HT receptors without causing stimulation. In the case of other drugs, *e.g.* tryptamine and high doses of 5HT itself, blockade follows activation and involves specific receptor desensitisation.

Serotonin antagonists acting on peripheral structures belong to two categories; those that block 5HT effects on smooth muscle and those that preferentially block peripheral neural responses. However, a substance known to act as a 5HT antagonist at one site cannot be assumed to act similarly at another. For instance, none of the common 5HT antagonists, *e.g.* methysergide, pizotifen and cyproheptadine, which antagonise 5HT effects on peripheral nerves, acts as a 5HT antagonist at sites in the brain where 5HT has been identified as a transmitter and where the effect of 5HT is inhibitory.[11] This does not necessarily mean that such "peripheral" 5HT antagonists cannot act centrally, since methysergide can block 5HT responses in a wide range of central sites where, however, there is no evidence of physiological involvement of 5HT, and the meaning of the antagonism is therefore far from clear. The number of agents with pharmacological properties of serotonin antagonism is quite large. However, only a few are safe to be used clinically and these are described below.

1. Ergotamine

The drug belongs to the family of ergot alkaloids, which are metabolites of the fungus *Claviceps purpurea*. Powdered fungus-infected rye was used in midwifery in the 17th century and was introduced into scientific medicine two centuries later. Chemically, the drug is a lysergic acid molecule with an amino-alcohol, amino-propranol radical on the carboxyl group. In small doses, the drug sensitises the smooth muscle of several tissues and organs to the effect of 5HT and noradrenaline, and causes vasoconstriction mostly in the carotid vascular bed, predominantly through alpha-adrenoceptor stimulation. On the other hand it antagonises the vasoconstrictive effects of 5HT on the rabbit ear artery and prevents re-uptake of monoamines by tissues. In general, in small doses the drug acts as an alpha-adrenergic and 5HT agonist, whilst in large doses it behaves as an antagonist.[12]

Dihydroergotamine (DHE) is the hydrogenated product of ergotamine, with similar properties which are only quantitatively different from the parent compound. Thus DHE has less intrinsic vasoconstrictor activity than ergotamine, yet its inhibitory effects on the CNS, facilitatory effect on the release of sympathetic transmitter substance and alpha-adrenoceptor antagonism are all greater.[13] It exerts a more pronounced effect on capacitance vessels than ergotamine and is therefore more useful in the treatment of postural hypotension. The constrictor action of both ergotamine and DHE is more marked in the external than the internal carotid territory and this is true both in the monkey[14] and in the human.[15]

Clinical use

Ergotamine has been used for the treatment of migraine for sixty years now. It has stood the test

of time and is generally accepted to be effective in 75-80% of cases. Its use is restricted to the treatment of the acute attack. Studies in migraine patients suggest that a good therapeutic response can be obtained with peak plasmal levels of 0.2 ng/ml within 1 hour of its administration, and that this is more reliably achieved if ergotamine is adminished parenterally or inhaled rather than when taken by the oral or rectal route.[16] The drug is usually combined with caffeine which increases its absorption, enhances its vasoconstrictive effects and increases both cAMP and catecholamines by inactivating their degrading enzymes, phosphodiasterase and catechol-*O*-methyl transferase, respectively. Oral and rectal preparations are also combined with an antihistamine or a sedative to reduce nausea, vomiting and agitation.

Side-Effects:
The most common are generalised muscle aches, nausea, vomiting, drowsiness and confusion. Daily use of ergotamine leads to rebound headaches, as the effect of the drug ceases a few hours after it is taken. Ths leads to further medication producing a vicious circle, which can only be broken by a carefully supervised withdrawal of the drug. The headaches are treated with analgesics together with a short period of high dose steroids, in an effort to restore the responsiveness of the cranial vessels to vasoactive substances, by removing the supersensitivity of the receptors due to prolonged over-stimulation by the daily administration of the drug.[17]

2. Methysergide
This compound is a semi-synthetic derivative of the naturally occurring ergometrine and consists of a lysergic acid nucleus and an amide side chain. Whilst lysergic acid diethylamide (LDS) possesses very strong 5HT antagonism, it is also a potent hallucinogen. On the other hand, 1-methyl-D-lysergic acid butanolamide (methysergide) has none of the psychotropic effects of LSD, and is four times more potent as a 5HT antagonist.[18]

1. The drug has certain pharmacological properties of its own, over and above those of 5HT antagonism. These include:
   (a) a weak oxytocic effect,
   (b) anticonvulsant action, varying from species to species, and
   (c) vasoconstrictive action on the carotid vascular bed of the monkey, most marked in the external carotid territory and potentiation of the constrictor effect of noradrenaline on the same vascular bed in the dog.[20]
2. 5-Hydroxytryptamine antagonism. The drug blocks a wide variety of responses to 5HT both *in vivo* and *in vitro*.
   (a) Vascular effects. Methysergide antagonises 5HT induced constrictor responses on the cranial arteries and more so in the internal than the external carotid circulation.[14] Small doses potentiate the vasoconstrictor effect of noradrenaline on the external carotid circulation in the monkey,[14] dog[20] and the isolated human temporal artery.[21]
   (b) Anti-inflammatory effects. Injected subcutaneously the drug inhibits edema induced by 5HT in the hind paw of anesthetised rats,[18] and pre-treatment of human subjects with methysergide will inhibit the sterile inflammatory response produced by the intracutaneous injection of manganese butyrate.[22]
   (c) Pulmonary effect. Methysergide, and to a lesser extent serotonin, when injected into the pulmonary artery of sheep caused a rise in pulmonary arterial pressure, pulmonary vascular resistance and frictional ("airways") resistance of the lungs. If the amine was administrated after methysergide was given, its effects were completely suppressed.[23]
   (d) CNS effects. The sedative effect of thiopental in mice is enhanced by 5HT and this effect is antagonised by pre-treatment with methysergide, whilst a similar potentiation of thiopental action by chlorpromazine cannot be prevented by the drug.[24] The effect, therefore clearly indicates that the drug is a specific 5HT antagonist.
   (e) Uterine effects. After pre-treatment *in vivo* with methysergide, the isolated rat uterus is refractory to serotonin stimulation, whilst the drug also protects pregnant mice against the deleterious effects of 5HT.[25]

Clinical Use
Once it was appreciated that migraine attacks are associated with low plasma serotonin, and the observation made that ergotamine tartrate has anti-serotonin properties, the way was paved for the introduction of serotonin antagonists in the prophylaxis of migraine. Methysergide was the first such drug to be introduced for that purpose and had certainly stood the test of time. Numerous clinical trials so far have confirmed its effectiveness in the prevention of migraine. Generally speaking, the drug reduces the frequency of migraine headaches.

by more than 50% in about 65% of patients, whilst one-third of those improved become almost headache free.[26] The dose required for this degree of improvement varies between 4 and 6 mg methysergide daily, in divided doses.

Side Effects

It has been estimated that about 10% of patients are unable to tolerate the drug because of persistent side effects, referrable mainly to the gastrointestinal and cardiovascular systems. An additional 30% have unpleasant symptoms in the form of epigastric discomfort or muscle cramps, which are mild and transient, disappearing in a few days or weeks.[26] Nearly always, side effects are dose-related, appear early in the course of treatment and subside on withdrawal of the drug. The major side-effects are as follows.

1. Vascular constriction, which declares itself as muscle cramps on exercise, at rest or even as pallor and coldness of the extremities with reduced or absent pulses.[27] Although mostly dose related, vasoconstrictive phenomena also appear in minor form in patients taking as little as 1 mg of the drug, suggesting that they could well be due to an idiosyncrasy on the part of the patient.
2. Epigastric discomfort is common in patients with a previous history of peptic ulceration, the mechanism being increase in basal HCl secretion by the drug.
3. Nausea is another common symptom and its mechanism may well be due to gastric hyperacidity.
4. Other less common, but nonetheless not so rare symptoms include vomiting, diarrhea, constipation, drowsiness, leg edema, mental confusion, arthralgias, falling hair and weight gain.
5. Fibrotic reactions. Retroperitoneal fibrosis is the commonest of such reactions but fibrosis of the pleura and cardiac valves has also been reported. It has been estimated that about 100 cases of retroperitoneal, pleural and cardiac fibrosis have occurred in about half-million patients treated with methysergide.[28] Since the introduction of one month's rest from treatment in every five to permit resolution of any impending fibrosis, only few cases have been reported. The fibrotic complications of methysergide are similar to those seen in patients with the carcinoid syndrome. Whether drugs which have antiserotonin properties and which simulate the action of serotonin on receptors have the potential of producing fibrotic reactions, remains a matter for conjecture.

The nature and mechanism of side effects, make it clear that methysergide should be avoided in patients with peripheral vascular disease, ischemic heart disease and peptic ulceration. Hypertension and thrombophlebitis are perhaps relative contraindications.

3. Pizotifen

The drug has a benzocycloheptathiophene nucleus with a side chain resembling that of cyproheptadine. It is 14 times as powerful as methysergide in neutralising a lethal dose of 5HT in the guinea pig, and three times as potent in counteracting diarrhea produced by endogenous 5HT in the mouse. In contrast to methysergide, the drug causes no vasoconstriction and no potentiation of 5HT, noradrenaline or histamine on the isolated human temporal or rabbit ear artery, although it causes a reduction of the constrictor effects of these drugs, but not of the ergot derivatives on the above arteries.[21] Pizotifen is a particularly potent inhibitor of the effect of histamine on dog blood pressure, guinea-pig bronchioles, rat paw edema, isolated guinea-pig ileum and rabbit auricular artery, and in that sense it acts as an H_1 receptor antagonist.[7] In high concentrations, it neither constricts peripheral blood vessels nor does it sensitise them to the action of these vasoconstrictor agents.[21]

Clinical Use

Pizotifen was introduced into clinical use for the prevention of migraine because of its antiserotonin effect. Whilst not as effective as methysergide for the purpose, it is widely used owing to lack of significant side-effects. Rates of improvement in different trials varies from 40% at doses of 1.5 mg daily to 70% with higher doses (3 mg daily).[29] The drug has also been found quite useful in controlling the diarrhea of the carcinoid syndrome, whilst at the same time reducing the excretion of 5-hydroxyindoleacetic acid.

Side Effects

The most frequent are drowsiness and increased appetite resulting in weight gain. Other less common side-effects that are complained of include mental depression, vertigo and aching muscles. Increased appetite is thought to be due to hypoglycemia as a result of either inhibition of glycogenolysis in the liver,[30] or through increased insulin secretion.[31]

4. Cyproheptadine

This drug is chemically related to pizotifen, in that it also possesses a tricyclic nucleus, except that the thiophene ring of pizotifen is substituted by a

TABLE 2
Diseases in which Serotonin May Play a Role and the Effect of Serotonin Antagonists

Disease	5HT Blood Levels	Role of 5HT in Disease	Effect of Antagonists
Carcinoid syndrome	High	Certain	Beneficial
Migraine	Low (during attack)	Probable	Beneficial
Raynaud's disease	Local increase	Possible	Aggravation
Hypertension	Unknown	Possible	Not proven
Mental disease	Variable	Probable	Doubtful
Dumping syndrome	High	Probable	Beneficial
Nociception	Low tissue content (brainstem)	Probable	Not proven

phenol ring. It possesses similar anti-serotonin and antihistamine properties. It resembles pizotifen in nearly all of its pharmacological effects.

It is a matter of great relevance to mention at this point that the release of growth hormone in the human is mediated through serotoninergic pathways, in view of the fact that small doses of the 5HT precursor, 5-hydroxytryptophan, will stimulate release of the hormone, and high levels of it are also found in patients with the carcinoid syndrome who have high circulating levels of 5-hydroxytryptophan.[32] Cyproheptadine, in doses used for prophylactic purposes in migraine, 8 to 12 mg per day, has been shown to inhibit release of growth hormone in the human by about 50%. The situations under which testing took place were insulin-induced hypoglycemia and standardised exercise for 20 minutes.[33] Similar results were obtained with cyproheptadine and methysergide by another group of workers.[34] It is generally thought that the site of action of the drugs is on the hypothalamus, although a direct effect on the pituitary gland itself cannot be excluded. On the other hand, pizotifen does not appear to have similar inhibitory effects on growth hormone release, in spite of its structural and pharmacological similarities to cyproheptadine.

The practical inference of these observations is that antiserotonin drugs, in particular cyproheptadine and methysergide should be prescribed with caution, if at all, for the prevention of migraine in children and adolescents.

Clinical Use

The drug is used as:

1. Antihistamine: in the treatment of pruritic dermatoses, hay fever, *etc.*
2. Antiserotonin: for the control of serotonin-induced symptoms of carcinoid, particularly the diarrhea. It was widely used in migraine, producing improvement rates of 43%, but appears to have been displaced by pizotifen, which is somewhat more effective and better tolerated.[26]
3. Appetite stimulant: however, its inhibitory effect on growth hormone release should be kept in mind, when used in children.

Side Effects

These are identical to those of pizotifen, *i.e.* drowsiness and weight gain due to increased appetite.

5. Lisuride

The drug is sterochemically related to D-isolysergic acid and has the generic name of lisuride hydrogen maleate. As a serotonin antagonist it is not as effective as methysergide and its main site of action appears to be the peripheral blood vessels. Whereas most ergot alkaloids induce pressure reactions, lisuride has a slight hypotensive effect when given to humans.

Lisuride has been used mostly in the prevention of migraine. In an open trial the drug reduced headache frequency by at least 50% in 34% of patients, whereas in the placebo group a similar reduction was noted by 32% of patients.[26] In two subsequent trials the response rate was 53% and 54% respectively.[35,36] Side effects recorded were nausea, vomiting, dizziness, muscular weakness and sleep disturbances and their incidence was lower than that of methysergide. It would appear that the drug may be useful in migraine prevention, has fewer side effects than methysergide and, unlike it, has not been known to cause retroperipheral fibrosis. However, its efficacy in migraine has not been proven convincingly. Lisuride is not available in Australia for clinical use.

6. Mianserin

This is a tetracyclic antidepressant compound, introduced for the purpose because of its lack of anticholinergic and cardiotoxic effects. It is said to be as effective in depression as the corresponding tricyclic drugs. It is a potent serotonin antagonist at peripheral receptors and it is highly likely that it interferes with serotoninergic transmission with the brain.[37] Side effects commonly complained of

TABLE 3
Serotonin Antagonists in Migraine Prophylaxis
Details Relating to Their Clinical Use

Drug	Age Suitable	Dose	Response Rate	Common Effects	Common Contraindications
Ergotamine (with phenobarbitone and belladona)	Children	1 b.i.d.-t.i.d.	50%	Mild drowsiness	Allergy to barbiturates
Propranolol	Adults Children	40 mg t.i.d.-t.i.d. 10 mg b.i.d.	65%	Tiredness Insomnia Hypotension	Asthma Heart failure Diabetes
Pizotifen	Adults	0.5 mg b.i.d. + 1 mg nightly (alternatively 2 mg nightly)	50%	Drowsiness Weight gain	Nil
Cyproheptadine	Adults	4 mg t.i.d.	43%	Drowsiness Weight gain	Nil
Methysergide	Adults	1 mg t.i.d.-2 mg t.i.d.	70%	Gastric irritation Peripheral vascular or coronary ischemia	Peptic ulcer Peripheral vascular or coronary disease

are drowsiness and fatigue; serious complications include agranulocytosis, which is usually reversible on cessation of the drug, whilst few causes of marrow depression have resulted in death.[38] As a result its use in clinical medicine remains uncertain.

7. Ketanserin

This compound is a quinazolinedione and is available as the tartrate salt, which is water soluble. Considerable amount of knowledge has been accumulated regarding its pharmacological actions.

In man, the drug decreases elevated systemic and pulmonary blood pressures by reducing peripheral resistance, whilst it has no effect in normotensive subjects. Digital vein constriction induced by 5HT is prevented by oral or IV ketanserin and so is cold-induced vasoconstriction in Raynaud's disease. Serotonin induced platelet aggregation can be prevented by ketanserin, and activated platelets assume normal aggregation indices after administration of the drug.[39] In common with cyproheptadine and methysergide, ketanserin will inhibit 5HT induced aggregation of human and cat platelets but has no effect on their ability to take up monoamines. Unlike cyproheptadine and methysergide, the drug is devoid of 5HT antagonism in the rat fundus and the guinea pig ileum. It acts mostly as a pure antagonist, devoid of mixed agonist-antagonist properties. Further, it is a selective $5HT_2$ antagonist, as it blocks some of the known peripheral actions of the amine, particularly impairment of the micro-circulation and increased vascular resistance. It is also a weak H_1 and alpha-adrenergic receptor antagonist. The main indications for use therefore become arterial hypertension, peripheral vascular disease and cardiopulmonary emergencies.[8]

Clinical Use

The drug is not available for general use worldwide. It is currently undergoing clinical trials in the treatment of essential hypertension and peripheral vascular disease. So far the drug has been found to be effective in both conditions.[40]

Side Effects

These are generally mild. They include drowsiness, mostly in the initial few days of treatment, dizziness, headache, nausea, weakness and epigastric discomfort. Their frequency and intensity is related to the size of the individual rather than the total daily dose. Most adverse reactions are transient and occur during the first few weeks of administration, whilst they are rare during chronic treatment.

The effect of serotonin antagonists on the more common diseases in which serotonin is thought to play a role is shown in Table 2, and their effectiveness in the prevention of migraine in Table 3.

SUMMARY

The realisation that serotonin plays a role not only in the carcinoid syndrome but also in migraine, nociception, dumping syndrome, vascular disease and hypertension, has led to an enormous amount of activity in search of serotonin antagonists.

Numerous such pharmacological agents have been identified but only few have found their way into clinical use. All of them are competitive serotonin inhibitors, in that they vie for the same receptor as the amine itself and are thus able to block its action as well as imitate its effects.

By far the widest use of such inhibitors is in the prevention of migraine, where they have effectively eliminated the dread of an attack from the life of the majority of patients. Whilst useful in the control of diarrhea in patients with carcinoid and dumping syndromes, their role in these diseases is limited. However, the possible role of serotonin in hypertension and nociception opens new avenues in the use of existing serotonin antagonists and calls for the discovery of a new generation of such pharmacological agents for the control of these conditions.

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