

گیرنده‌های سروتونین - به کجا می‌روند؟

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چکیده:

سی‌وسه سال پیش، گادوم و پیکارآی گیرنده‌های سروتونین ایلئوم کوچکه هندی را بر اساس اثرات در بلوک انقباضات عضلات صاف D و M مهاری تقسیم (و M) روده‌ای ناشی از سروتونین، به انواع دی‌بنزیلین (در مغز، به طبقه بندی 10° زیر D مورفین کردند. در پی آن، تعیین موضع $5-HT$ گونه جایگاه‌های اختصاصی اتصال به لیگاند برای در مغز رت منجر شده‌است. گرچه اهمیت عملکردی بسیاری از گیرنده $5-HT$ این زیرگونه‌ها مورد مناقشه است، شواهدی وجود دارند که نشان می‌دهند این گیرنده‌ها را می‌توان بر اساس ماهیتشان در کوپل شدن با و یا $5-HT1$ و $5-HT2$ پیامبرهای ثانویه زیرگروهی کانالهای یونی، به دو گروه عمده تقسیم کرد. بر این مبنا باشند $5-HT1$ به نظر می‌رسد گیرنده‌های (و یا فسفا از G که از طریق آدنیلات سیکلاز (اغلب زیرگونه‌های خانواده گیرنده‌های وابسته به پروتئین شناخته) عمل می‌کنند. M (که امروزه تحت نام $5-HT3$ تبدیل اینوزیتول $5HT2$ گیرنده‌های مرکزی (زیرگونه‌های می‌شوند) به نظر می‌رسد متعلق به خانواده بزرگ کانالهای یونی باشند که توسط لیگاند باز و بسته می‌شوند. در فراهم آمدن امکان تقسیم‌بندی زیرگونه‌های گیرنده سروتونین به عنوان مولکولهای پروتئینی خاصی که توسط ژنهای ویژه‌ای رمزگردانی می‌شوند، تکنیک کلون‌سازی این گیرنده‌ها اهمیت بسزایی داشته‌است. مسئله‌ای که امروزه با آن مواجهیم این است که بین تغییراتی که در فعالیت سلولی زیرگونه‌های مختلف گیرنده سروتونین رخ می‌دهند با کثرت تغییرات رفتاری که در پی اثرات سروتونین در مغز بوجود می‌آیند، ارتباطی پیدا کنیم. مقاله حاضر خلاصه‌ای است در باره نقش در تنظیم حرارت، تعدیل عملکرد دستگاه قلبی - عروقی، اختلالات غذاخوردن، اختصاصی زیرگونه‌های گیرنده خواب، فعالیت $5-HT$ جنسی، حالات اضطرابی، پرخاشگری، اسکیزوفرنی و افسردگی، ضمن اینکه چکیده‌ای از رابطه بین این گیرنده‌ها و دخالت احتمالی آنها در اتیولوژی بیماریهای مذکور ارائه می‌شود.

کلید واژه‌ها: ۱- سروتونین

۲- زیرگونه‌های گیرنده

۴- اختلالات اضطرابی

۵- افسردگی

۳- خواب

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سال سوم / شماره ۱ و ۲ / بهار و تابستان ۱۳۷۵

SROTPECER RECEPTORS AND THEIR POSSIBLE FUNCTION IN THE BRAIN

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ABSTRACT

Thirty-three Years ago, Gaddum and Picarelli classified the serotonin receptors in the guinea pig ileum into D and M types based on the activity of dibenzylamine (D) and morphine (M) to block contractions of intestinal smooth muscle caused by serotonin. The subsequent location of specific ligand binding sites for serotonin in the brain has led to the identification of ten serotonin receptor sub-types in rat brain. The cloning of these receptor sub-types has been of importance in enabling them to be classified as specific protein molecules encoded by specific genes. The problem now arises with regard to the linking of the changes in the cellular activity of the various receptor sub-types with the plethora of behavioural changes that arise as a consequence of the actions of serotonin in the brain.

The present review summarizes the evidence implicating the role of specific serotonin receptor sub-types in sleep, anxiety states, schizophrenia and depression. A summary of the relationship between these receptor sub-types and their possible involvement in the aetiology of these diseases is also given.

Keywords: 1) Serotonin 2) Receptor subtypes 3) Sleep
4) Anxiety disorder 5) Depression

INTRODUCTION

Over a century ago, a substance was recognized in clotted blood which was found

to cause vasoconstriction. This substance was still present following adrenalectomy therapy suggesting that it differed from

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adrenaline and noradrenaline. Eventually, Rapaport, Green and Page in 1947, purified the vasoconstrictor factor from serum and identified it as serotonin ("serum tonic"). Independently of the American investigators, Erspamer and colleagues in Italy had identified a substance they termed "enteramine" from the intestine. "Enteramine" was subsequently found to be identical to serotonin⁽²⁵⁾ and was subsequently synthesized by Hamlin and Fisher in 1951. Chemically, serotonin or enteramine is the indoleamine 5-hydroxytryptamine (5-HT).

Following the isolation and synthesis of serotonin in the early 1950's, there has been increasing interest in the physiological function of this amine. Initially it was assumed that its main function was that of a peripheral hormone because of the relatively high concentrations that were found in the gastrointestinal tract and blood. Twarog and page⁽⁶⁷⁾ soon showed, however, that it was also present in the mammalian brain thereby suggesting that it may have a neurotransmitter role there⁽²⁾. Interest in the physiological role of serotonin in the central nervous system has pre-occupied neurobiologists since that time.

The detection of serotonin in nervous and non-nervous tissue was aided by the development of the Falck-Hillarp histochemical technique, a method whereby freeze-dried sections of tissue, when

exposed to formaldehyde, vapour causes indoleamines to emit a yellow fluorescence. Dahlstrom and Fuxe⁽¹⁶⁾ used this technique to show that highest concentration of serotonin in the brain is located in the raphe nuclei, projections from these cell bodies ascending to the forebrain via the medial forebrain bundle. Descending fibres were also shown to project to the dorsal and lateral horns and the intermediolateral column of the spinal cord.

Detailed observation of the distribution of the serotonergic system in the brain became possible with the development of specific antibodies to the amine⁽⁶⁴⁾ and the introduction of autoradiographic methods for both the human⁽³⁸⁾ and rodent⁽⁵⁸⁾ brain.

For serotonin to be considered as a neurotransmitter, it was essential to establish that it produced its physiological effects by activating specific receptors located on the intestinal wall, platelet membrane or on nerve cells. A major development occurred in 1957 when Gaddum and Picarelli⁽²⁶⁾ showed that the action of serotonin on the guinea pig ileum could be blocked by either phenoxybenzamine (dibenzylamine) or morphine.

These investigators termed the two types of serotonin receptors on the intestinal wall "D" (for dibenzylamine) or "M" (morphine) receptors, the "M" type receptors being associated with the nerves supplying the intestine that produced contraction of the

smooth muscle by facilitating acetylcholine release while the "D" receptors were located on the smooth muscle wall. More recently, it has been realized that the "D" receptors are widely distributed in the body and coincide with 5HT₂ receptors which, when activated by selective agonists, contract smooth muscle and aggregate platelets. They also occur in synaptosomal membranes where they are possibly associated with post-synaptic membrane structures⁽²⁴⁾. By contrast, the "M" receptor has not been unequivocally identified in neuronal membranes. However, increasing evidence now suggests that the peripheral "M" receptor is identical to the 5HT₃ receptor in the brain⁽⁶⁾. Thus in a period of some 20 years, the distribution of serotonin in both nervous and non-nervous tissue has been determined, many of its physiological properties explained and the types of receptors upon which it acts to produce its diverse physiological effects evaluated.

5-HT Receptor SUB-Types

Current knowledge of 5HT receptors has been derived from advances in medicinal chemistry, from the synthesis of ligands that show considerable specificity for sub-population of 5HT receptors. The application of such ligands to our understanding of the distribution of the 5HT receptor sub-types has been largely due to quantitative invitro autoradiographic emiss-

sion tomography. Functional studies undoubtedly lag behind but the development of sophisticated electrophysiological techniques and studies of changes in secondary messenger systems which respond to the binding of selective ligands to the 5HT receptor sub-types have opened up the probability that the physiological importance of the numerous receptor sub-types will soon be clarified.

As a consequence of the application of these various techniques, the International Union of pharmacological Societies (IUPHAR) Commission on Serotonin nomenclature has published two major reports which attempt to classify the various receptor sub-types according to their ligand binding properties and secondary messenger systems⁽⁶⁾. The first report classified 5HT receptors into 5HT₁-like (comprising 5HT_{1A}, 1B, 1C and 1D) 5HT₂ (formerly the 5HT-D receptor) and 5HT₃ (formerly the 5HT-M receptor). The detection of a novel 5HT receptor, that could not be classified as 5HT₁, 5HT₂, or 5HT₃, in both the peripheral and central nervous systems by Dumuis et al.^(22,23), extended the receptor types to 5HT₄. The application of molecular biology techniques has led to the cloning and sequencing of at least six different 5HT receptors namely 5HT_{1A}, 5HT_{1B}, 5HT_{1C}, 5HT_{1D}, 5HT₂, and 5HT₃⁽³⁸⁾. Further studies of the second messenger systems to which these receptors sub-types

are attached have shown that the 5HT1-like, 5HT2 and 5HT4 receptors belong to the G protein coupled receptor superfamily, whereas the 5HT3 receptor belongs to the same family as the nicotinic, GABA-A and glycine receptors which are ion gated channel receptors.

The most recent publication of the IUPHAR Commission has re-defined the 5HT receptor subtypes according to their second messenger associations and thereby helped to stress the functional role of the receptor sub-types rather than relying primarily on the specificities of ligands that bind to them ⁽³⁹⁾. This approach has led to the classification of 5HT receptors into those linked to adenylate cyclase (5HT1A, 5HT1B, 5HT1D, 5HT4), those linked to the phosphatidyl inositol system (5HT2A, 5HT2B and 5HT2C), and those linked directly to ion channels (5HT3). Table 1 summarizes the accepted classification of the 5HT receptor sub-types together with their anatomical location and the most specific agonists and antagonists which have been developed.

More recently the family of 5HT receptors has been dramatically increased to include 5HT4, 5HT5A and 5B, 5HT6 and 5HT7. Of these, only the 5HT4 receptor has so far not been cloned ⁽³²⁾. Of these newly discovered receptors, only the 5HT4, receptor has so far been investigated in some detail. These receptors are quite

widely distributed in the brain and peripheral tissues where they are positively coupled to adenylate cyclase. In the brain, the 5HT4 receptors facilitate acetylcholine release and may play a role in peristalsis. It has been hypothesized that in the brain 5HT₄ receptors may also play a role in facilitating cholinergic transmission and thereby have a potential role to play in presenting cognitive deficits which are associated with cortical cholinergic malfunction ⁽⁵⁾. The possible clinical significance of 5HT4 receptors must await the development of specific agonists and antagonists. So far, such compounds have not been developed.

Despite the dramatic advances which have taken place in the identification and characterisation of 5HT receptor sub-types, it is evident that many of the ligands used to characterise these receptor sub-types are not completely selective. It must also be emphasized that receptors are the products of genes which are therefore subject to genetic changes and, as a consequence, variability in physiological and pharmacological responsiveness. Thus affinity, potency and intrinsic activity of a drug at one receptor may vary depending on the time, species and receptor-effector coupling. It is already known, for example, that ipsapirone, buspirone, spiroxatrine and lysergic acid diethylamide may behave either as agonists or antagonists depending on the functional model being used to assess their

**TABLE 1. CLASSIFICATION OF CENTRAL
SEROTONIN RECEPTORS IN MAMMALIAN BRAIN**

RECEPTOR SUB-TYPE					
5HT-1A	5HT-1B	5HT-1D	5HT-1E	5HT-1F	
<i>5HT1-LIKE</i>					
<i>Secondary messenger</i>		-	<i>cAMP</i>	-	-
<i>Clones</i>	<i>Human</i>	<i>Rat</i>	<i>Human</i>	<i>Human</i>	<i>Human</i>
<i>Amino acids</i>	421	386	377/390	365	366
<i>Selective agonists</i>	8-OHDPAT	CP93129	Sumatriptan	-	-
<i>Selective antagonists</i>	Way 100135	-	-	-	-
<i>Radioligands</i>	³ H-8OHDPAT	¹²⁵ I GTI	¹²⁵ I GTI	³ H-5HT	¹²⁵ I LSD

CP-93129 = 5-hydroxy-3-(4-1,2,5,6-tetrahydropyridyl)-4-azarindole

8-OHDPAT = 8-hydroxy-2-(di)-n-propylaimino-tetralin

WAY 100135 = N-test-butyl-3-4 (2-methoxyphenyl)piperazin-1-YI-2-phenyl- Propanamide dihydrochloride)

GTI = 5-0-carboxamidomethylglycyl(¹²⁵I) tyrosinamide-tryptamine.

RECEPTOR SUB-TYPE	5HT2A*	5HT2B	5HT2C**	5HT3***	5HT4
<i>Secondary messenger</i>	-	IP ₃ /DG	-	Cation channel	<i>cAMP</i>
<i>Clones</i>	<i>Human</i>	<i>Rat fundus</i>	<i>Human</i>	<i>Mouse</i>	-
<i>Amino acids</i>	471	479	458	487	-
<i>Selective agonists</i>	-Methyl-5HT	-methyl-5HT	-methyl-5HT	2-methyl-5-HT	5-methoxy-tryptamine Renzapride
<i>Selective antagonists</i>	Ketanserin Ritanserin LY53857	LY53857	Mesuler-gine LY53857	Tropisetron Granisetron Ondansetron	GRII3808
<i>Radioligands</i>	³ H-Ketanserin	³ H-5HT	³ H-mesulergine	³ H-zacopride	³ H-GR113808

LY= 4-ISO-propyl-7-methyl-9-(2-hydroxy-1 methylpropyl carbonyl-4,6 ,6A,7,8,9,10A - octahydroindolo (4,3,FG).

GR 113808 = (1-(2-(Methylsulphonyl-amino) ethyl)-4-piperidinyl) methyl-1-methyl-IH indole-3-carboxylate).

* *5HT2A previously called "5HT2" or "5HT D" receptor*

** *5HT2C previously called "5HTIC" receptor*

*** *5HT3 previously called "5HTM" receptor*

(Table 1 abridged from Humphrey et al., 1993)

Legend to Table 1.

<i>8-OHDPAT</i>	= <i>Dipropylamino-8hydroxy-1,2,3,4-tetrahydronaphthylene</i>
<i>RU-24969</i>	= <i>5-Methoxy-3-(1,2,3,6-tetrahydrophyridin-4-yl) IH indol.</i>
<i>MCPP</i>	= <i>1-(3 chlorophenyl) piperazine</i>
<i>TFMPF</i>	= <i>1-(metrifluoromethylphenyl) piperazine</i>
<i>DOI</i>	= <i>1-(2,5-dimethoxy-1-iodophenyl) 2-aminopropane</i>
<i>MDL 73005</i>	= <i>8,2(2,3-dihydro-1,4-benzodioxin-2yl) methylamino-ethyl-8-azaspirol (4,5) decan -7,9-dione</i>
<i>NAN 190</i>	= <i>1-(2-methoxyphenyl) 4-(4(2-phthalimido) entyl-peierzine.</i>
<i>5-CT</i>	= <i>5-carboxamidotryptamine</i>
<i>ICI 169369</i>	= <i>(2-(dimethylamino-ethylthio-3-phenylquinoline)</i>
<i>ICS 205-930</i>	= <i>(3-tropanyl)-IH-indole-2-carboxylic acid ester</i>
<i>DOM</i>	= <i>2,5, dimethoxy-4-dimethylbenzene ethamine</i>

(See reviews by Leysen, 1985; Fraser et al., 1990).

activity. A similar problem arises with intrinsic activity which is usually assumed to be a direct reflection of the pharmacological properties of the drug. It seems possible that the affinity can also be influenced by the nature of the genetically determined receptor-effector coupling and therefore tissue (and species) dependent. Such factors

may help to explain why the identification and sub-classification of 5HT receptor sub-types is complex and often confusing.

This dilemma can be illustrated by the attempts being made to identify the functional role of 5HT receptor sub-types using ligands which are believed to be specific in their binding properties. Such

ligands may prove to be non-selective, more selective for and as yet unidentified 5HT receptor sub-type or more selective for non-5HT receptor site. Conversely several non-5HT ligands are known to bind to 5HT receptors with a high affinity. For example, the alpha 1 adrenoceptor antagonist WB4101, and the beta adrenoceptor

antagonist pindolol, have a high affinity to 5HT1A receptors. Nevertheless, despite these cautions, there is a growing body of information which implicates different 5HT receptor sub-types in a variety of physiological and pharmacological responses and these will be briefly reviewed.

Table 2. SEROTONIN RECEPTOR SUB-TYPES AND DISEASE STATES

<i>PHYSIOLOGICAL OR PATHOLOGICAL CONDITION</i>	<i>SEROTONIN RECEPTOR SUB-TYPE IMPLICATED</i>
1. Feeding behaviour	<i>5HT1A agonists enhance food consumption in experimental animals. 5HT2 agonists decrease food consumption in experimental animals.</i>
2. Thermoregulation	<i>5HT1A agonists cause hypothermia in experimental animals. 5HT1B and 5HT2 agonists cause hyperthermia in experimental animals.</i>
3. Sexual behaviour	<i>5HT1A agonists both facilitate and inhibit sexual behaviour in male rats. 5HT1B agonists inhibit sexual behaviour in the male but facilitate the behaviour in the female rat.</i>
4. Cardiovascular system	<i>5HT1, 5HT2 and 5HT3 receptors maybe involved in the complex action of serotonin on blood pressure 5HT2 agonists appear to be hypertensive agents whereas the antagonists are hypotensives.</i>
5. Sleep	<i>5HT1A agonists delay the onset of REM sleep while 5HT2 antagonists suppress REM sleep.</i>
6. Hallucinogenic activity	<i>Most "classical" hallucinogens such as LSD and mescaline are antagonists at 5HT2 receptors.</i>

7. Antipsychotic activity *Many atypical neuroleptics (e.g. amperozide and risperidone) are 5HT2 receptor antagonists. In animals, 5HT3 antagonists have profiles similar to chronically active neuroleptics.*
8. Anxiolytic activity *Several novel anxiolytics (e.g. buspirone, ipsapirone) are 5HT1A partial agonists. HT2 and 5HT3 antagonists have anxiolytic properties.*
9. Depression *5HTA receptors are functionally sensitized by chronic antidepressant treatments in rats. 5HT2 receptor numbers are increased and activity decreased, in depression, return to control values in response to treatment.*

Sleep

It has been known for some years that the functional activity of 5HT neurons in the brain changes dramatically during the sleep-wake arousal cycle⁽⁴⁸⁾. Thus from a stable, slow and regular discharge pattern during quiet waking, neuronal activity gradually declines as the animal becomes drowsy and enters slow wave sleep. During rapid eye movement (REM) sleep, 5HT activity is totally suppressed but in anticipation of awakening the neuronal activity returns to its basal level several seconds before the end of the REM episode. During arousal or waking, the 5HT neuronal discharge pattern increases considerably above the quiet waking state⁽⁴¹⁾.

Koella⁽⁴⁵⁾ has reviewed the evidence implicating the involvement of serotonin in the sleep-wake cycle but the involvement of specific serotonin receptor sub-types in sleep mechanisms is unclear. Experimental evidence suggests that 5HT1A agonists

delays the onset of rapid eye movement (REM) sleep while 5HT2 antagonist suppress REM and have variable effects on non-REM sleep⁽⁵⁶⁾.

It must be emphasized that most studies of the relationship between the serotonergic system and sleep have been conducted in rats and therefore the relevance of such findings to man remains unproven. From such experimental studies, it has been shown that blockade of 5HT2 receptors increases the proportion of slow wave sleep and decreases the quantity of REM sleep⁽⁶⁸⁾. Whether this effect of 5HT2 antagonists can be ascribed to a specific effect on slow wave sleep is however, a matter of conjecture as any increase in time spent in one stage of sleep will be reflected in a decrease in the time spent in other stages of sleep. However, experimental evidence suggests that most drugs that alter serotonergic transmission reduce REM sleep⁽²¹⁾. There is evidence that the 5HT2 antagonist

ritanserin improves sleep quality in those suffering from "jet-lag" (37) Which suggests that the 5HT2 receptors may be involved in adjusting the sleep-wake cycle to the photoperiod. Furthermore, experimental data suggest that activation of 5HT2 receptors may vary according to the sleep/wake cycle (20). Such findings suggest that 5HT2 receptors are involved in the regulation of circadian rhythms and the sleep-wake cycle. With regard to the overall role of 5HT in sleep, Koella (45) has postulated that serotonin may produce its various effects on sleep architecture by influencing cognition and vigilance.

Hallucinogenic activity

There is abundant experimental evidence to show that serotonin plays a major role in the mechanism of action of hallucinogens (42, for review), but it is presently unclear whether the actions of hallucinogens can be explained by their agonistic or antagonistic actions. LSD, for example, may behave either as an agonist or antagonist depending on the particular tissue, concentration and experimental condition, whereas the tryptamine type of hallucinogens usually act as agonists (30). Experimental evidence nevertheless suggest that the behavioural effects of a number of indole alkylamine (e.g. LSD-like) and phenylalkylamine (e.g. mescaline-like) hallucinogens can be attenuated by 5HT2A antagonists and that the potency of these

classes of hallucinogens at 5HT2A (and possibly 5HT2C) sites correlate with their hallucinogenic potency in man (31). It seems unlikely however that all hallucinogens owe their activity to their potency in stimulating 5HT2A receptors; LSD and 5-methoxydimethyltryptamine for example interact with 5HT2C sites, while phenylclidine may owe its hallucinogenic potency to an action on NMDA and a sub-class of sigma receptors (43). Nevertheless, the balance of evidence suggest that most "classical" hallucinogens like LSD, mescaline and psilocybin act as partial agonists on 5HT2A receptors.

Drug abuse

The role of 5HT in the control of alcohol intake has received considerable attention following the discovery that 5HT reuptake inhibitors reduce alcohol intake in alcohol dependent rats (39,53). Similar effects have been found for intra-cerebroventricularly administered 5HT or its precursor 5HTP (60). Regarding the type of 5HT receptor involved, there is experimental evidence that the 5HT1A partial agonists buspirone and gepirone (12) are effective. Differences were found between the effects of the 5HT3 antagonist ondansetron and the 5HT2A/5HT2C antagonist ritanserin. Thus ondansetron reduces alcohol intake without effecting the alcohol preference of rats while ritanserin reduces both the alcohol

preference and intake⁽⁴⁹⁾. This suggests that, at least in rats, different populations of 5HT receptors may be involved in alcohol intake and preference.

Regarding other types of drugs of abuse, the 5HT₃ antagonist MDL 72222 has been shown to block place preference conditioning induced in rodents by morphine or nicotine without affecting the preference for amphetamine⁽⁴⁴⁾. It is possible that these effects of 5HT₃ antagonists are associated with the reduction in dopamine release as it is well established that the rewarding effects of many drugs of abuse are due to increased dopaminergic activity in limbic regions⁽¹⁸⁾. On the strength of the experimental findings, it has been proposed that 5HT₃ antagonists might be useful to treat drug abuse in man⁽⁹⁾. Only appropriate placebo controlled studies of 5HT₃ antagonists will clarify the therapeutic value of such agents in different types of drug abuse.

Antipsychotic activity

Given the complexity of the serotonergic system and its interaction with multiple neurotransmitter systems in the mammalian brain, it is not surprising to find that 5HT plays a role in the aetiology of Schizophrenia. Meltzer⁽⁵⁰⁾ has suggested that in schizophrenia a malfunction of the mechanism whereby 5HT modulates the release of dopamine (for example, due to the

decreased inhibition by 5HT of the release of dopamine in the mesencephalon and frontal cortex) might contribute to the enhanced neocortical dopaminergic function which probably forms the biochemical basis of the disease. The antipsychotic activity of atypical neuroleptics such as clozapine and risperidone may therefore lay in the normalization of the relationship between the malfunctioning 5HT and dopaminergic systems.

The novel antipsychotic drug clozapine has a very complicated neurochemical profile in that it has a high affinity for 5HT_{2A}, 5HT_{2C}, 5HT₃, 5HT₆ and 5HT₇ receptors in addition to its action on D₄ and D₃ receptors (see⁵⁹). Risperidone likewise has a high affinity for 5HT_{2A} receptors as well as acting as an antagonist of D₂ receptor⁽⁵¹⁾. Such drugs have received attention recently because of their reduced propensity to cause extrapyramidal side effects and for their efficacy in treating the negative symptoms of schizophrenia. These properties may partly reside in the antagonistic actions of the atypical neuroleptics on the various sub-populations of 5HT receptors of which the 5HT_{2A} receptor may be of primary importance.

In experimental studies, many clinically effective neuroleptics have been shown to act as 5HT_{2A} receptor antagonists⁽³⁰⁾. Studies on post-mortem brain from schizophrenic patients have shown that the

decrease in the number of 5HT_{2A} receptors in the prefrontal cortex might be related to the disease process⁽⁵²⁾. It therefore seems unlikely that the antipsychotic activity of neuroleptics can be explained solely in terms of their action on 5HT_{2A} receptors. Furthermore, no correlation exists between the average therapeutic doses of a neuroleptic and its affinity for 5HT_{2A} receptors. It does seem possible, however, that several atypical neuroleptics such as amperozide, risperidone and possibly ritanserin do owe at least part of the pharmacological profile to their ability to inhibit 5HT_{2A} receptors.

Following the discovery that selective 5HT₃ antagonists reduce the behavioural effects of the infusion of dopamine into the nucleus accumbens, there has been considerable interest in the possible role of 5HT₃ receptor antagonists as potential neuroleptic agents⁽³³⁾. This subject has been extensively reviewed by Costall and co-workers⁽¹⁴⁾ and while there is a growing body of evidence to suggest that 5HT₃ antagonists may be therapeutically valuable for the treatment of disorders of the gastro-intestinal tract, as antiemetics and possibly anxiolytic agents, there is currently little evidence to suggest that such drugs are effective in the treatment of schizophrenia. The experimental studies of the 5HT₃ antagonists on dopamine (D₁) autoreceptors which may eventually offer new leads to

the development of novel antipsychotic drugs has been the subject of recent mini reviews by Abbott⁽¹⁾ and Tricklebank⁽⁶⁶⁾.

Anxiolytic activity

Although the benzodiazepine anxiolytics primarily interact with the GABA receptor complex, there is ample experimental evidence to show that secondary changes occur in the turnover, release and firing of 5HT neurons as a consequence of the activation of the GABA-benzodiazepine receptor. Similar changes are observed in the raphe nuclei where a high density 5HT_{1A} receptors occur (see⁶²). Such findings suggest that 5HT may play a key role in anxiety disorders.

Gardner⁽²⁸⁾ has reviewed the literature implicating the involvement of serotonin in anxiety. Undoubtedly one of the most important advances in this area has been the development of the azaspirodecanone derivatives buspirone, gepirone and ipsapirone as novel anxiolytics (see⁶⁵). All three agents produce a common metabolite, namely 1-(2-pyrimidinyl) piperazine or 1-PP, which may contribute to the anxiolytic activity of the parent compounds. It soon became apparent that these anxiolytic agents do not act via the benzodiazepine or GABA receptors but show a relatively high affinity for the 5HT_{1A} sites; the 1-PP metabolite however only possesses a very low affinity for the 5HT_{1A} site although it

may contribute to the anxiolytic effect of the parent compound by acting as an alpha₂ adrenoceptor agonist. In experimental studies, these atypical anxiolytics have mixed actions, behaving as agonists in some situations and antagonists in others. For this reason they are considered to be partial agonists at 5HT_{1A} receptors, acting either as agonists on pre-synaptic 5HT_{1A} receptors or antagonists on post-synaptic 5HT_{1A} receptors ⁽¹⁹⁾.

In animal models of anxiety, 5HT₂ receptor antagonists have been shown to be active. Ritanserin appears to exhibit both anxiolytic and anxiogenic activity in different animal models ⁽²⁷⁾. Nevertheless, in man, preliminary evidence suggests that ritanserin is an effective anxiolytic agent ⁽¹⁰⁾, although Deakin et al. ⁽¹⁷⁾, in a placebo controlled trial of the 5HT₂ antagonist ritanserin, reported no differences in the Hamilton Anxiety and the Clinical Global Impression Scales between the drug treated and placebo treated patients.

The anxiolytic properties of 5HT₃ receptor antagonists have been demonstrated in several animal models of anxiety ⁽⁵³⁾. In these models, the 5HT₃ antagonists mimic the anxiolytic effects of the benzodiazepines but differ from the latter in their lack of sedative, muscle relaxant and anticonvulsant action. These compounds appear to be extremely potent (acting in the ng-ug/kg range) and, providing the initial

clinical finding of their anxiolytic activity is substantiated, this group of drugs could provide a valuable addition to the non-benzodiazepine anxiolytics. Thus experimental and clinical evidence suggest that 5HT_{1A} receptor partial agonists, 5HT₂ and 5HT₃ antagonists may be useful and novel anxiolytic agents.

Aggression, panic attack and related disorders

The possible overlap between anxiety, depression, panic attack, aggression and obsessive compulsive disorders, and the involvement of serotonin in the symptoms of these disorders, has recently led to the investigation of various selective serotonin uptake inhibitors and selective 5HT receptor agonists/antagonists in the treatment of these conditions. In experimental studies, there is evidence that drugs such as eltopazine, which binds with high affinity to 5HT_{1A}, 5HT_{2B} and 5HT_{2C} sites, are active anti-aggressive agents, whereas selective 5HT_{1A} agonists, and 5HT₂ and 5HT₃ antagonists are inactive ⁽⁵⁵⁾. There is also preliminary evidence to suggest that selective serotonin uptake inhibitors such as fluoxetine reduce impulsive behaviour which may contribute to their therapeutic action in the treatment of obsessive compulsive disorders and possibly in reducing suicidal attempts.

Zohar and Insel ⁽⁷⁰⁾ have suggested that

the symptoms of obsessive compulsive disorder are due to supersensitive 5HT1 type receptors and that the function of serotonin uptake inhibitors such as clomipramine, fluoxetine and the non-selective 5HT antagonist metergoline owe their efficacy to their ability to reduce the activity of these receptors. The effects of serotonin uptake inhibitors in the treatment of obsessive compulsive disorders has been critically reviewed by Zak et al (69).

It now seems generally accepted that the effects of anti-obsessional drugs may be mediated by serotonergic mechanisms. The apparent hypersensitivity of obsessive compulsive patients to the trazodone metabolite m-chlorophenyl piperazine (MCCP, a non-selective 5HT1B, 5HT2C) and 5HT2 agonist) suggests that a diverse group of 5HT1 and 5HT2 receptors are involved (71). The efficacy of buspirone, a partial agonist of 5HT1A receptors in attenuating the obsessional symptoms (57) further suggests that 5HT1A receptors are also involved. As the 5HT re-uptake inhibitors such as fluoxetine and fluvoxamine are particularly effective in attenuating the obsessive symptoms following several weeks of administration, it may be argued that the therapeutic effect of such drugs lies in their ability to desensitize the supersensitive 5HT1-type receptors. Which of the 5HT1 receptors is specifically involved is unclear, but neuroimaging studies

on patients with obsessive compulsive disorder implicates the striatum as the major brain region which is defective (4). The 5HT receptors in the striatum are of the 5HT1D and 5HT2 in man which may implicate these receptor sub-types specifically in the aetiology of the condition.

There is increasing evidence that selective serotonin uptake inhibitors are of value in the treatment of panic attack (61) and while the specific involvement of serotonin in the aetiology of the disease has yet to be established, there is experimental evidence which suggests that the 5HT2 receptors on the platelet membrane are hypoactive (7). Effective treatment with antidepressant or behaviour therapy results in a partial normalization of 5HT2 receptor responsiveness. Whether selective 5HT2 antagonists have any therapeutic value in the treatment of this disorder still awaits confirmation.

5HT Receptors and the anxiety disorders

Coplan and co-workers (11) have postulated that the neurological basis for the role of 5HT in anxiety disorders involves two major serotonergic pathways. The raphe projections to the brain stem and limbic system mediate the main inhibitory effects of 5HT whereas those projections for the raphe to the hypothalamus mediate the stimulatory endocrine effects of the

transmitter. Loss of serotonergic tone is postulated to be associated with depression and panic. This implies that panic attacks prefrontally involve the descending inhibitory pathways to the medullary centres which leads to the symptoms of suffocation frequently experienced by such patients. The non effectiveness of 5HT_{1A} partial agonists such as buspirone in panic disorder may therefore be related to the inability of such drugs to suppress the consequent ventilatory "overdrive". By contrast depressive symptoms may be related to the loss of serotonergic tone in the ascending projections to the limbic and cortical regions of the brain. Such defects may be corrected by drugs such as the azaspirodecanones (ipsapirone, buspirone etc) and the antidepressants (tricyclics and selective serotonin reuptake inhibitors SSRI 's) which activate the postsynaptic 5HT_{1A} receptors in these regions.

With regard to generalized anxiety disorder⁽¹¹⁾ postulate that an overactivity of the stimulatory 5HT pathways occur. Drugs such as buspirone and ipsapirone are effective in such conditions because they stimulate the inhibitory 5HT_{1A} auto receptors on the raphe nuclei and thereby reduce serotonergic function. It is noteworthy that the SSRI 's often worsen anxiety initially because they temporarily enhance serotonergic function. Adaptive changes in the pre-and post synaptic 5HT

receptors then occur leading to a reduction in the anxiety state.

Depression

Serotonin is believed to play a multi-functional role in depression which is to be anticipated from its involvement in the physiological processes of sleep, mood, vigilance, feeding and possibly sexual behaviour and learning all of which are deranged to varying extents in severe depression. However, the involvement of precise serotonin receptor sub-types in depression, and in the action of antidepressants, is still far from clear. One approach to unravelling the changes in serotonin receptors in depression has been to study the effects of chronically administered antidepressants on serotonin receptor sub-types in rat brain. While there is evidence that most antidepressants show only a low affinity for the 5HT₁ sites, there is experimental evidence to show that chronic antidepressant treatment results in a hypersensitivity of post-synaptic and a hyposensitivity of pre-synaptic 5HT_{1A} receptors⁽³⁴⁾. In contrast to the 5HT_{1A} receptors, many antidepressants from various chemical classes have a moderate affinity for 5HT₂ receptors although there is no apparent correlation between the 5HT₂ receptor affinity and the antidepressant potency⁽⁵⁴⁾.

Regarding the changes that occur in rat

cortical 5HT₂ receptor density following chronic antidepressant and lithium treatment, there is unequivocal evidence that the number of receptors increase in response to chronic drug treatment although it must be emphasized that chronic ECS results in a decrease in the receptor number. Similarly in untreated depressed and panic patients, the density of 5HT₂ receptors on the platelet membrane has been shown to be increased^(7,8). The number of receptors normalizes on effective, but not ineffective, treatment. Using the serotonin induced platelet aggregation response as a measure of the functional activity of 5HT₂ receptors, it has been consistently shown that the 5HT₂ receptor responsiveness is reduced in the untreated depressive but returns to control values following effective treatment irrespective of the nature of treatment^(8,36). Thus changes in 5HT₂ receptor density and function appear to be disturbed in the depressed patient and return to control values only following effective treatment. The increase in the receptor number, and decrease in their responsiveness to serotonin, in the untreated depressed patient may suggest an abnormality in the coupling mechanism between the receptor site and the phosphatidylinositol second messenger system that brings about the platelet shape change underlying aggregation.

Deakin et al⁽¹⁷⁾ have suggested that

depression could arise from a pathological enhancement of 5HT₂ receptor function. This view would concur with the observations that the functional activity of 5HT₂ receptors on the platelet membrane is enhanced in depression^(8,36) and the increase in the density of 5HT₂ receptors in the frontal cortex of brains from suicide victims^(3,63). Deakin et al⁽¹⁷⁾ hypothesize that enhanced 5HT₂ receptor function is associated primarily with anxiety, a common feature of depression, and that the increased activity of the 5HT₂ receptors results in an attenuation of the functioning of 5HT₁ receptors thereby resulting in the symptoms of depression. Whether this change in the activity of 5HT₁ receptors is due to direct effect of the altered 5HT₂ receptor function is uncertain. There is evidence that hypercortisolaemia, which is a characteristic feature of depression, reduces the activity of these receptors probably through central glucocorticoid type 2 receptors⁽¹⁷⁾. Clearly further research is needed to determine the precise interaction between the 5HT₂ and 5HT₁ receptor types.

More recently,⁽¹¹⁾ have speculated that the 5HT_{1B/1D} receptors may have a role to play in depression and in the mode of action of antidepressants. These receptors appear to be located pre-synaptically where they control the release of 5HT; in experimental studies the non-selective 5HT₁ antagonist methiothepin has antidepressant properties

(⁴⁷ unpublished). Thus it may be speculated that the 5HT_{1B}/ID receptors are supersensitive in depression, thereby leading to a reduced intersynaptic concentration of 5HT with a consequent increase in the number of post-synaptic 5HT₂ receptorsites. However, only, the development of highly selective 5HT_{1B}/ID antagonists will enable this hypothesis to be tested.

Although the precise mechanism whereby antidepressants produce their therapeutic effects is incompletely understood, there is a growing body of evidence to suggest that serotonin receptors, particularly of the 5HT_{1A} and 5HT₂ sub-type, play a role in their actions. Only the 5HT₂ receptors has, so far, been convincingly demonstrated to be malfunctioning in depression and to be normalized following effective treatment. Leonard (⁴⁶) has reviewed the role of biological markers of 5HT receptors in depression elsewhere.

Conclusion

It is evident that serotonin is involved in a variety of physiological processes and that disturbances of serotonergic function may be of importance in the aetiology of many gastrointestinal, cardiovascular and central

nervous system diseases. The existence of sub-types of serotonin receptors and the impetus that this has given to the development of drugs with selective actions on these receptor sub-types is already leading to the development of new therapeutic agents. Evaluation of the functional status of serotonin receptor sub-types in psychiatric and neurological diseases may be of future importance in the diagnosis and assessment of treatment response in such patients. In this regard, the development of serotonin receptor probes coupled with such techniques as positron emission tomography may be of considerable importance in diagnosis in the future (¹⁵).

To-date, at least 4 major sub-types of serotonin receptor have been described and a major advance has been made with the isolation of genomic clones for these receptor sub-types. This has been reviewed by (^{32,35,40}). We now await the further development of selective ligands for all the serotonin receptor subtypes which may ultimately lead to a better understanding of the functional significance and clinical relevance of serotonin receptors in health and disease.

REFERENCES

- 1) Abbott, A. (1990). 5HT₃ antagonists and ligands for dopamine D₁ and auto-receptors offer new leads for antipsychotic drugs. *Trends in Pharmacological Sciences*, 11, 49-51.
- 2) Amin, A.H., Crawford, T.B.B. and Gaddum, H.H. (1954). The distribution of substance P and 5-hydroxytryptamine in the central nervous system of the dog. *Journal of Physiology* 816-695, 621.
- 3) Arora, R.C. and Meltzer, H.Y. (1989). Serotonergic measures in brains of suicide victims: 5HT₂ binding sites in the frontal cortex of suicide victims and control subjects. *American Journal of Psychiatry*, 146, 730-736.
- 4) Baxter, L.R., Thompson, J.M. and Schwartz, J.m. (1987). Trazodone treatment response in obsessive compulsive disorder correlated with shifts in glucose metabolism in the caudate nucleus. *Psychopathology* 20 (Supplement 1), 114-122.
- 5) Bockert, J., Ford, J.R., Dumuis, A. and Clarke, D.E. (1992). The 5HT₄ receptor: a place in the sun. *trends in Pharmacology Science* 13, 141-145.
- 6) Bradley, P.B., Engel, G., Feniuk, W., Fozard, J.R., Humphrey, P.P.A., Middlemiss, D.N., Mylecharane, E.J., Richardson, B.P. and Saxena, P.R. (1986). Proposals for the classification and nomenclature of functional receptors for 5-hydroxytryptamine. *Neuropharmacology*, 25, 563-576.
- 7) Butle, J., Tannion, M., O 'Bourke, D., Fahy, T.J. and Leonard, B.E. (1988a). Functional changes in the adrenergic and serotonergic systems in patients with panic disorders. IN: *Progress in Catecholamine Research, Part C: Clinical Aspects*, pp. 399-407.
- 8) Butler, J., Tannian, M. and Leonard, B.E. (1988b). The chronic effects of desipramine and sertraline on platelet and synaptosomal 5HT uptake in olfactory bulbectomized rats. *Prog. Neuropsychopharmacology and Biological Psychiatry*, 12, 585-594.
- 9) Carboni, E., Aqua, E., Frau, R. and Di Chiara, G. (1989). Differential inhibitory effects of a 5HT₃ antagonist on drug induced stimulation of dopamine release. *European Journal of Pharmacology*, 164, 515-519.
- 10) Ceulemans D., Hoppenbrouwers, M., Gelders, Y. and Reyntjens, A.J.M. (1985). The influence of ritanserin, a serotonin antagonist, in anxiety disorders: a double-blind placebo-controlled study vs. lorazepam. *Pharmacopsychiatry*, 18, 303-305.
- 11) Chopin, P., Moret, C. and Briley, M. (1994). In vivo neuropharmacology of 5HT_{1B/D} receptor ligands. *Pharmacology Therapeutics* (in press).

12) Collins, D.M. and Myers, R.D. (1984). Buspirone attenuates volitional alcohol intake in chronically drinking monkeys. *Alchol* 4, 49-56.

13) Coplan, J.D., Walk, S.I. and Kelin, D.F. (1995). Anxiety and the 5HT_{1A} receptor. IN: *Psychopharmacology: The Fourth Generation of Progress* (Eds. F.E. Bloom and D.J. Kupfer). Raven Press, New York, pp. 1301-1310.

14) Costall, B., Naylor, R.J. and Tyers, M.B. (1988). Recent advances in the neuropharmacology of 5HT₃ antagonists and antagonists. *Revs. Neuroscience.*, 2, 41-65.

15) Cros, A.J. (1988). Serotonin in neurodegenerative disorders. IN: *Neuronal Serotonin*, (Eds. N.N. Osborne and M. Harmon). Pub. J. Wiley and Sons, Chichester, pp. 231-254.

16) Dahlstrom, A. and Fuxe, K. (1964). Evidence for the existence of monoamine containing neurons in the central nervous system. *Acta Physiologica Scandinavia*, 62, Supplement 232, 1-55.

17) Deakin, J.F.W, Guimaraes, F.S., Wang, M and Hensman r. (1991). Experimental tests of the 5HT receptor imbalance theory of affective disturbance. (Eds. M. Sandler, A. Coppen, and S. Harnett). Pub. Oxford University Press, Oxford, pp. 143-154.

18) Di Chiara, G. and Impreto, A. (1988). Drugs abused by humans preferentially

increase synaptic dopamine concentrations in the mesolimbic system of freely moving rats. *Proceedings of the National Academy of Science, USA*, 85, 5274-5278.

19) Dourish, C.T. (1987). Brain 5HT_{1A} receptors and anxiety. IN: *Brain 5HT_{1A} Receptors*. (Eds. C.T. Dourish, S. ahlenius and P.H. Hudson). Pub. Ellis Horwood, Chichester, PP. 261-277.

20) Dugovic, C., Leysen, L.E., Janssen, P.F.M. and Wauquier, A. (1989a). The light/dark cycle modulates the effects of ritanserin on sleep wakefulness patterns in the rat. *Pharmacology, Biochemistry and Behaviour*, 34, 533-537.

21) Dugovic, C., Wauquier, A., Leysen, J.E., Marrannes, R. and Janssen, P.A.J. (1979b). Functional role of 5HT₂ receptors in the regulation of sleep and wakefulness in the rat. *Psychopharmacology* 97, 436-442.

22) Dumuis, A., Bouhelal, R., Sebben, M., Cory, R. and Bockaert, J. (1988). A non-classical 5-hydroxytryptamine receptor positively coupled with adenylate cyclase in the central nervous sytem. *Molecular Pharmacology*, 34, 880-887.

23) Dumuis, A., Sebben M. and Bockaert, J. (1989). The gastrointestinal prokinetic benzamide derivatives are agonists at the non-classical 5HT (5HT₄) positively coupled to adenylate cyclase in neurons. *N.S. Arch. Pharmacology*, 340, 403-410.

24) Engel, G., Hoyer, D., Kalkman, H.O.

and Wick, M.B. (1985). Pharmacological similarity between the 5HT_{1D}-receptor on the guinea pig ileum and the 5-HT binding site. *British Journal of Pharmacology*, 84, 1515-1520.

25) Erspamer, V. and Asero, B. (1952). Identification of enteramine, the specific hormone of the enterochromaffin cell system, as 5-hydroxy-specific hormone of the enterochromaffin cell system, as 5-hydroxy-tryptamine. *Nature*, 169, 800-801.

26) Gaddum, H.H. and Picarelli, Z.P. (1957). Two kinds of tryptamine receptor. *British Journal of Pharmacology*, 12, 323-328.

27) Gardner, C.R. (1986). Recent developments in 5HT related pharmacology of animal models of anxiety. *Pharmacology, Biochemistry and Behaviour*, 24, 1479-1485.

28) Gardner, C.R. (1988). Potential use of drugs modulating 5HT activity in the treatment of anxiety. *General Pharmacology*, 19, 347-356.

29) Gill, K. and Amit, Z. (1989). Serotonin uptake blockers and voluntary alcohol consumption: a review of recent studies. IN: *Recent Developments on Alcoholism*. (Ed. M. Galanter), Pub. Plenum Press, New York, pp. 225-248.

30) Glennon, R.A. (1985). Involvement of serotonin via the action of hallucinogenic agents. IN: *Neuropharmacology of*

Serotonin (Ed. A.R. Green), Pub. Oxford University Press, London, pp. 253-280.

31) Glennon, R.A. (1988). Site selective serotonin agonists and discriminative stimuli IN: *Transduction Mechanisms of Drugs stimuli*. (Ed. F.C. Colpaert and R.L. Balster), Pub. Springer Verlag, Berlin, pp. 16-31.

32) Glennon, R.A. and Dukat, M. (1995). Serotonin receptor sub-types. IN: *Psychopharmacology: The Fourth Generation of Progress* (Eds. F.E. Bloom, D.J. Kupfer), Raven Press, New York, PP. 415-430.

33) Hagan, R.M., Butler, A, Hill, J.M., Jordan, C.C., Ireland, S.J. and Tyers, M.B (1987). Effects of the 5HT₃ antagonist GR 38032F on responses to injection of a neurokinin agonist into the ventral tegmental area of the rat brain. *European Journal of Pharmacology*, 138, 303-305.

34) Hamon, M., Ereit, M.B., El Mestikawy, S., Verge, D, Daval, G., Marquet, A. and Gozlan, H. (1987). Pharmacological, biochemical and rat brain. IN: *Brain 5HT_{1A} Receptors*. (Eds. C.T. Ahlenius, S. and P.H. Hudson, Pub. Ellis Horwood Ltd., Chichester, pp. 34-51.

35) Hartig, P.R. (1989). Molecular biology of 5HT receptors. *Trends in Pharmacological Sciences*, 10, 64-69.

36) Healy, D., Carney, P.A. and Leonard, B.E. (1983). Monoamine-related markers of depression: changes following treatment. *Journal of Psychiatric research*,

17, 251-260.

37) Hoppenbrouwers, M.L., Vanden Bussche, g. and Gelders, Y. (1988). Is ritanserin a serotonin receptor blocker able to counteract jet lag? A placebo controlled pilot investigation. *Psychopharmacology* 96, (Suppl.) 245.

38) Hoyer, D.(1992). Agonists and antagonists at 5HT receptor subtypes. *Advances in Biosciences*, 85, 29-47

39) Humphrey, P., Hoyer, D. and Hamon, M.(1989). The classification of 5-hydroxytryptamine receptors. Serotonin Club Nomenclature Committee, Update No. 1.

40) Humphrey, P.P.A., Hartig, P. and Hoyer, D. (1993). A proposed new nomenclature for 5HT receptors. *Trends in pharmacological Science*, 14, 233-236.

41) Jacob, B.L. and Fornal, C.A. (1995). Serotonin and behaviour: a general hypothesis. IN: *Psychopharmacology: The Fourth Generation* and New York, pp. 461-469.

42) Jacobs, B.L. (1984). *Hallucinogens: neurochemical, behavioural and clinical perspectives*. Pub. Raven Press, New York.

43) Junien, J.L. and Leonard, B.e. (1989). Review: Drugs acting on sigma and phencyclidine receptors: A review of their nature, function and possible importance *Clinical Neuropharmacology*, 12, (13), 353-347.

44) Kilpatrick, G.J., Bunce, K.T. and

Tyers, M.b. (1990). 5HT3 receptors. *Medical Research Developments*, 10, 441-475.

45) Koella, W.P. (1988). Serotonin and sleep. IN: *Neuronal Serotonin*. (Eds. N.N. Osborne and M. Hamon), J. Wiley and Sons Ltd., pp. 153-170.

46) Leonard, B.E. (1995). Biological markers of serotonin receptors in depression and animal models of depression. *International Review of Psychiatry*, 7, 69-83.

47) Leonard, B.E. and Kelly, J. (1995). (Unpublished).

48) McGinty, D.J. and Harper, R.M. (1976). Dorsal raphe neurons: depression on firing during sleep in cats. *Brain research*, 101, 569-575.

49) Meert, T.F. (1993) Effects of various serotonergic agents on alcohol intake and alcohol preference in Wistar rats selected at two different levels of alcohol preference. *Alcohol and Alcoholism*, 28, 157-170.

50) Meltzer, H.Y. (1989). Clinical studies on the mechanism of action of clozapine: the dopamine-serotonin hypothesis of schizophrenia. *Psychopharmacology*, 99, S18-S27.

51) Meltzer, H.Y., Matsubara, S. and Lee, J.C. (1989). Classification of typical and atypical antipsychotic drugs on the basis of D1, D2 and 5HT2 pKi values. *Journal of Pharmacology and Experimental therapeutics*, 251, 238-246.

52) Mita, T., Hanada, S., Nishino, N., Juno, T., Nakai, H., Yamadori, t., Mizoi, Y. and Tanaka, C. (1986). Decreased serotonin S2 and increased dopamine D2 receptors in chronic schizophrenics. *Biological Psychiatry*, 21, 1407-414.

53) Myers, R.D. and Quartford, S.Q. (1991). Alcohol drinking attenuated by sertraline in rats with 6OHDA or 5,7 DHT lesions of the N. accumbens: a caloric response. *Pharmacology, Biochemistry and Behaviour*, 40, 923-928.

54) Ogren, S.O. and Fuxe, K. (1985). Effects of antidepressant drug on cerebral serotonin receptors. IN: *Neuropharmacology of Serotonin*, (Ed. A.R. Green, Pub. Oxford University Press, London, pp. 131-180.

55) Oliver, B. (1981). Selective anti-aggressive properties of DU-27725: ethiological analyses of intermale and territorial aggression in the male rat. *Pharmacology, Biochemistry and Behaviour*, 14, (Supplement 1), 61-67.

56) Pastel, R.H. (1988). Effects of Ly53857, a selective 5HT2 antagonist, on sleep in the rat. *Society of Neurosciences Abstracts*, 14, 1307.

57) Pato, M.T., Pigott, T.A., Hill, J.L., Grover, G., Bernstein, S.E. and Murphy, D.L. (1989). Clomipramine versus buspirone in OCD; A controlled trial. *American Meeting of the American Psychiatric Association*, San Francisco,

Abstract, No. 14.

58) Pazos, K a., Engel, G. and Palacios, J.M. (1985). Beta-adrenoceptor blocking agents recognize a sub-population of serotonin receptors in rat brain. *Brain research*, 343, 403-408.

59) Roth, B.L., Craigo, S.C. and Chondhary, M.S. (1994). Binding of typical and atypical antipsychotic agents to 5HT6 and 5HT7 receptors. *Journal of Pharmacology and Experimental Therapeutics*, 268, 1403-1410.

60) Sellers, E.M., Higgins, G.A. and Sobell, M.G. (1992). 5HT and alcohol abuse. *Trends in Pharmacology Science*, 13, 69-75.

61) Sheehan, D.V., Zak, J.P., Miller, J.A., and Fanous, B.S.L. (1988). Panic disorder: the potential role of serotonin reuptake inhibitors. *Journal of Clinical Psychiatry*, 49, (Supplement), 30-36.

62) Sleight, A.J., Perce, P.A., Schmidt, A.W., Hekmatpanah, C.R. and Peroutka, S.J. (1991). The clinical utility of serotonin receptor active agents in neuropsychiatric disease. IN: *Serotonin Receptor Sub-Types: Basic and Clinical Aspects*. (Ed.S. Peroutka), Pub. Wiley-Liss Inc., New York, pp. 211-227.

63) Stanley, M. and Mann, J.J. (1983). Increased serotonin 2 binding sites in frontal cortex of suicide victims. *Lancet*, i, 214-216.

64) Steinbusch, H.W.M. (1981).

Distribution of serotonin-immuno-reactivity in the central nervous system of the rat cell bodies and terminals. *Neuroscience*, 6, 557-618.

65) Traber, J. and Galser, T. (1987). 5HT_{1A} receptor related anxiolytics. *Trends in Pharmacological Sciences*, 8, 432-437.

66) Tricklebank, M.D. (1989). Interactions between dopamine and 5HT₃. *Trends in Pharmacological Sciences*, 10, 127-129.

67) Twarog, B.M. and Page, I.H. (1953). Serotonin content of some mammalian tissues and urine and a method for its determination. *American Journal of Physiology*, 175, 157-161.

68) Wilkinson, L.O.L. and Dourish, C.T. (1991). Serotonin and animal behaviour. IN: *Serotonin Receptor Sub-types: Basic and*

Clinical Aspects. (Ed. S.J. Peroutka), Pub. Wiley Liss, Inc., New York, pp. 147-210.

69) Zak, J.P., Miller, J.A., Sheehan, D.V. and Fanous, B.S.L. (1988). The potential role of serotonin reuptake inhibitors in the treatment of obsessive compulsive disorder. *Journal of Clinical Psychiatry*, 49, (Supplement), 23-30.

70) Zohar, J. and Insel, T.R. (1987). Obsessive-compulsive disorders: psychobiological approaches to diagnosis, treatment and pathophysiology. *Biological Psychiatry*, 22, 667-687.

71) Zohar, J., Mueller, E.A., Insel, T.R., Zohar-Kadouch, R.C. and Murphy, D.L. (1987). Serotonergic responsivity in obsessive-compulsive disorder: comparison of patients and healthy controls. *Arch. General Psychiatry*, 44, 946-951.