The Serotonin System Part II: Pharmacological Interventions

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ABSTRACT

There is increasing evidence that alterations in the serotonin system may mediate various psychiatric dysfunctions. By directly influencing and modifying either the specific receptor implicated in the dysfunction, or the serotonin system generally, success with treatment has been demonstrated.

Price et al. have proposed a method for classifying pharmacological interventions which affect the serotonin system.[6] The five groups of agents (precursors, releasers, reuptake inhibitors, receptor agonists, and receptor antagonists) act in different ways, which in part, accounts for their efficacy in treatment or prevention of psychiatric illness. This paper will review the medications which modulate serotonin production, resorption or interaction at the receptor level. The clinical implications of such modulation, and the success of such psychopharmacologic treatment will be assessed with respect to a variety of common psychoadaptive conditions.

The underlying assumption of this psychopharmacologic approach is that the dysregulation of certain neurotransmitters, in particular serotonin, results in the expression of certain psychopathologies. Success with agents which directly or indirectly effect the serotonin system provides some support for this hypothesis.

Key Words: *5-hydroxytryptamine, pharmacology, psychiatry, serotonin*

RÉSUMÉ

De plus en plus d'indications semblent montrer que le système de la sérotonine pourrait agir comme médiateur dans la manifestation de divers troubles psychiatriques. Ainsi, on a constaté qu'il est possible de soigner ces troubles en agissant directement et en modifiant le récepteur précis à l'origine du trouble, ou le système de la sérotonine en général.

Price et ses collaborateurs proposent une méthode pour classifier les interventions pharmacologiques relatives au système de la sérotonine. Les cinq groupes d'agents (précurseurs, libérateurs, inhibiteurs du recaptage, agonistes du récepteur et antagonistes du récepteur) fonctionnent différemment, ce qui explique en partie leur efficacité pour le traitement ou la prévention des problèmes psychiatriques. Le présent document passe en revue les médicaments qui modifient la production de sérotonine, sa résorption ou son interaction avec le récepteur. Les incidences cliniques d'une telle modulation et le succès d'un traitement psychopharmacologique seront analysés selon diverses conditions habituelles de psycho-adaptation.

L'hypothèse sous-jacente à l'approche psychopharmacologique est que le dérèglement de certains neuromédiateurs, en particulier la sérotonine, entraîne l'expression de diverses psychopathologies. L'utilité des agents qui agissent directement ou indirectement sur le système de la sérotonine semble appuyer cette hypothèse.

Mots clés: *5-hydroxytryptamine, pharmacologie, psychiatrie, sérotonine*

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It has been postulated that certain psychiatric illnesses, as detailed in Part I, may arise due to dysfunction of the serotonergic system (Table I).[1] Studies have suggested that patients with markedly reduced concentrations of 5-HIAA (the main serotonin metabolite) in cerebro spinal fluid (CSF) are more prone to violent suicide attempts than control subjects.[2] It has also been reported that patients suffering from depression and impulse control disorders have dysfunctions of the serotonergic system which can be detected through 5-HIAA metabolite assays.[3,4]

Such studies have led to the speculation that agents which specifically target the serotonergic system may facilitate treatment of psychiatric illnesses. Numerous traditional psychopharmacologic agents (such as the tricyclic antidepressants) have serotonergic activity. Many serotonin-specific medications (including fluoxetine and ondansetron) have recently been marketed; many more (such as ritanserin and ipsapirone) await further trial and study. Use of these medications has increased our understanding of the serotonin system and its role in the development of psychiatric illness.[5]

There are at least five ways in which drugs are thought to affect the serotonergic system (Table II). The first of these ways is through the administration of precursors. These are substances from which serotonin may be synthesized, such

Table I: Receptor Functional Significance and Pharmacologic Manipulation*

Indication	Serotonin Receptor(s)	Medications
Depression	5-HT_{1A}, 5-HT_{2A}, 5-HT_{2B}	5-HT Reuptake Blockers 5-HT_{1A} Agonists MAO Inhibitors 5-HT Precursors
Anxiety	5-HT_{1A}, 5-HT_{2A}, 5-HT_3	5-HT_{1A} Agonists 5-HT_3 Antagonists
Appetite Regulation	5-HT_{1A}, 5-HT_2	5-HT Reuptake Blockers 5-HT_2 Antagonists MAO Inhibitors 5-HT Releasers
Obsessive-Compulsive Disorder	unknown	5-HT Reuptake Blockers
Acute Migraine	5-HT_{1D}, 5-HT_{1C}	5-HT_{1D} Agonists
Mixed Anxiety-Depressive Disorder	5-HT_{2A}, 5-HT_{2B}, 5-HT_{1A}	5-HT_2 Antagonists 5-HT_{1A} Agonists
Sleeping Disorders	unknown	5-HT Precursors
Panic Disorder	? 5-HT_{1A} ?	5-HT_{1A} Agonists
Chemotherapy-induced Emesis	5-HT_3	5-HT_3 Antagonists
Dysthymia	? 5-HT_2 ?	5-HT_2 Antagonists

* Adapted from Price et al. *J Clin Psych* 1990; 51 (Suppl):31-41[6]

Table II: Summary of Serotonergic Medications

Group	Examples
Precursors	L-Tryptophan 5-Hydroxytryptophan (5-HTP)
Releasers	Fenfluramine
Reuptake Blockers	Tricyclic Antidepressants (e.g., Clomipramine Amitriptyline) Fluoxetine/Fluvoxamine Sertraline MAO Inhibitors (e.g., Phenelzine)
5-HT Agonists	Metachlorophenylpiperazine (mCPP — Trazodone Metabolite) Buspirone (5-HT_{1A} partial specific) Sumatriptan (5-HT_{1D})
5-HT Antagonists	Cyproheptadine (5-HT_2) Methysergide (5-HT_2) Ritanserin (5-HT_2) Ondansetron (5-HT_3) Granisetron (5-HT_3)

* Adapted from Price et al. *J Clin Psych* 1990; 51 (Suppl):31-41[6]

as the dietary amino acid progenitor of serotonin, L-tryptophan (L-TRP). Owing to its safety profile and predictable pharmacologic effects, numerous studies have used L-tryptophan to study the serotonergic system.[6]

L-Tryptophan, found in a wide variety of dietary sources, competes with other, large amino acids for uptake into the brain. It is then converted by the rate-limiting enzyme tryptophan hydroxylase into 5-hydroxytryptophan (5-HTP). In turn, 5-HTP is decarboxylated into 5-HT (5-hydroxytryptamine serotonin). It has been postulated that depression, among other conditions, may be partly due to a deficiency of serotonin[7] and thus, it would be possible to mediate an increased turnover of centrally produced and stored serotonin by supplementing dietary sources of tryptophan. This increased supply of serotonin would then act as an endogenous antidepressant. Clinical success with supplemental therapy has been limited, in large part due to the fact that there is a rate limiting enzymatic process at work, and excess amounts of dietary precursor will be simply excreted and wasted. Recently, some research has focused on the use of 5-HTP as a precursor, in order to bypass this rate-limiting enzyme, though results have been inconclusive.[8]

Serotonin is produced and stored presynaptically in granules. Releasers (for which fenfluramine is the prototype agent), promote release of this supply into the synapse. These agents may exert their therapeutic effects by quantitatively increasing the amount of serotonin available for receptor stimulation. It was thought that a large and relatively gradual release of serotonin into the synapse would be helpful in the treatment of depression, among other disorders. However, simply increasing the amount of neurotransmitter available may not always lead to desired therapeutic outcomes. Use of fenfluramine has demonstrated certain important biochemical limitations of this approach in treating dysfunctions of the serotonergic system.

There are currently eight named serotonin receptor sites, and many more putative receptors have been reported.[9] Each of these receptors affects a unique secondary messenger system; hence each receptor is thought to modulate unique neu-

rotransmitter outcomes.[10] For example, the 5-HT_{1A} receptor, when stimulated by serotonin, causes an inhibition of adenylate cyclase. The 5-HT_{1A} receptor, located presynaptically will therefore inhibit subsequent release of serotonin. By contrast, the 5-HT_2 receptors are thought to mediate turnover of phosphatidylinositol; stimulation of these postsynaptic receptors is excitatory for the serotonergic system generally. The same neurotransmitter, serotonin, will therefore exhibit dramatically different effects, depending upon which receptor sites are stimulated. Releasers, such as fenfluramine, are not sufficiently refined to target specific receptor sites; they simply increase available amounts of neurotransmitter within the synapse. This increased amount of serotonin may exert inhibitory effects (on the presynaptic 5-HT_{1A} receptor) or excitatory effects (on the postsynaptic 5-HT_2 receptors), but it is difficult to predict which one will predominate.

This model then explains the limited efficacy of releasers in the treatment of a wide variety of psychopathologies. Fenfluramine is indicated only as an anorexiant, and is of limited efficacy for the treatment of eating disorders. It has been used, though with limited success as an antidepressant, in patients refractory to traditional agents. The fact that fenfluramine indirectly causes stimulation of a wide variety of serotonin receptors also accounts for its relatively unfavourable side effect profile.

The reuptake inhibitors have analagous net effects as the releasers. Recall that the principal mechanism by which serotonin is removed from the synapse is through reuptake back into the presynaptic neuron. Many of the 'typical' antidepressants, such as amitriptyline, fluoxetine or clomipramine block this pre-synaptic reuptake, thereby effectively increasing the concentration of serotonin within the synapse.[11] Monoamine oxidase inhibitors, such as phenelzine block the activity of the major degredative enzyme within the synapse. Once again, simply increasing the amount of serotonin available within the synapse gives no indication whether it will act in an excitatory or inhibitory fashion.

The reuptake inhibitors appear to be more effective in a diverse range of psychopathologies, than the releasers. The clinical effects of reuptake inhibitors are, therefore, more complicated than their simple pharmacological effects. The older agents (e.g., amitriptyline, imipramine, clomipramine) are also potent reuptake inhibitors in the noradrenergic system; this in part explains their efficacy as not only antidepressants, but also in a variety of psychiatric dysfunctions such as panic disorder or obsessive-compulsive disorder. It is thought that tricyclic antidepressants, with a secondary substituent side chain show increased selectivity in inhibiting norepinephrine uptake. Conversely, those tricyclics with tertiary or quaternary side chain structures, or a 3-substituted halogen in the tricyclic nucleus will be more selective for inhibiting serotonin reuptake. Thus, small alterations in the tricyclic molecule may produce dramatically different effects in terms of reuptake inhibition. This in turn will help explain the different clinical indications for reuptake inhibitors. The balance of specificity for serotonin versus norepinephrine, and the relative potency of the reuptake inhibition are both important in developing any predictive model for efficacy of reuptake inhibitors generally, and tricyclic agents specifically.[12]

Many tricyclic compounds produce active metabolites *in vivo*. These metabolites often display specificity for one or the other biogenic amines, and this is often different than the parent compound. Imipramine, for example, is relatively equipotent in its inhibition of both serotonin and norepinephrine uptake. Imipramine's major metabolite, desipramine, preferentially blocks norepinephrine reuptake. Clomipramine shows increased specificity for the serotonergic system; desmethylclomipramine acts as a specific norephinephrine reuptake blocker. It is likely that the interaction between these two monoaminergic systems accounts for the efficacy of tricyclic reuptake inhibitors in the treatment of various psychopathologies. It is also likely that this interaction accounts for the side effect profile of tricyclic compounds.

Recently, there has been increasing interest in the 'serotonin-specific anti depressants', such as fluoxetine, fluvoxamine and sertraline. These non-tricyclic compounds are highly specific in their sertoninergic activity, and display little, if any, affinity for the noradrenergic system. A series of studies have demonstrated that acute administration of serotonin reuptake inhibitors causes an initial reduction in serotonin turnover. However, after approximately two weeks, there is a return to normal, control values. The mechanism for this decompensation reaction is not completely understood; it appears to be a factor in the activity of fluoxetine, fluvoxamine,[13] and sertraline.[14,15] The net result of this change in amine turnover is a stabilization of both the serotoninergic and the beta-adrenergic receptor systems. This stabilization appears to be essential for the antidepressant activity associated with reuptake inhibitors, whether they are 'serotonin-specific' or not.

With the discovery and elucidation of the serotonin family of receptors (5-HT_1, 5-HT_2 and 5-HT_3), there has been much research recently focused on the role of var-

ious receptor agonists and antagonists which can directly effect specific receptors for specific therapeutic outcomes. The functional significance of a variety of 5-HT receptors has been described, and targeting receptors responsible for the development of psychopathologies provides an effective method of treatment — without many of the side effect problems associated with 'broad spectrum therapy' such as reuptake inhibition.

Currently, the most widely available serotonin receptor agonist is metachlorophenylpiperazine (m-CPP), a metaboite of trazodone. This metabolite is a non-specific agonist, with activity at many pre- and post-synaptic serotonin receptor sites. Therefore, like the reuptake inhibitors, it is difficult to develop a predictive model for m-CPP's effects since it will stimulate both the excitatory post-synaptic and inhibitory pre-synaptic receptor sites. In many ways, m-CPP may act analagously to the reuptake inhibitors. Other receptor agonists, capable of activity at specific receptor sites will undoubtedly increase our understanding of the serotonergic system.

Several receptor antagonists are available, and the use of these agents has greatly increased our understanding of the role of the serotonergic system in the development of certain psychopathologies. As the name implies, the receptor antagonists directly block activation of 5-HT receptors. Non-selective agents, such as methysergide, cyproheptadine or metergoline have significant effects on multiple serotonin receptors, with enhanced activity at one specific receptor site (e.g., methysergide has potency and efficacy of the 5-HT_{1D} receptor site). The selective blocking agents exert their effects predominantly at one specific receptor (e.g., the 5-HT_3 antagonists ondansetron and granisetron). Ketanserin, a novel antihypertensive agent has potent effects on the S2 serotonin receptor in the smooth vessel vasculature.[16]

Buspirone is the first widely-available drug of the azapirone class. It possesses a novel chemical structure completely different from the benzodiazepines or antidepressants, and possesses a unique mechanism of action and side effect profile. Buspirone is thought to function as a partial agonist at the 5-HT_{1A} receptor site; evidence suggests that the azapirones may have dual antianxiety and antidepressant activity.[17] Owing to its bimodal nature, buspirone appears to be composed of both 5-HT_{1A} agonist and antagonist properties. The functional significance of its pharmacology may depend on the underlying neurophysiologic dysfunction.[18] In depressive states, when there appears to be a deficiency of serotonin output, azapirones may enhance expression of serotonin. Conversely, during times of overstimulation of serotonin neurotransmission (as is thought to occur during anxiety and panic states), azapirones may produce a functional antagonism of the serotonin system.[19] In net, the azapirones appear to work as serotonergic stabilizers, although further research is necessary to clarify the exact nature and functional significance of this potentially important new class of serotonin-active drugs.

The receptor agonists and antagonists offer several advantages over traditional antidepressants which act as reuptake inhibitors. Instead of increasing the amount of serotonin available in a non-specific way, these agents target unique and discrete receptors responsible for development of psychiatric dysfunction. Implicit in this approach is the idea that unique and discrete receptors are indeed responsible for the development of psychiatric dysfunction. This has yet to be confirmed, though clinical success with receptor-specific agents and empirical evidence seems to suggest this is true. However, equally likely is a complex, as yet undescribed interaction between serotonin and other monoaminergic systems. This latter possibility is one which has piqued the interest of numerous researchers.

The use of medications in the treatment of psychiatric dysfunctions has provided relevant information about the dysfunctions.[20] Specifically, the role of the monoaminergic neurotransmitter systems, such as serotonin, in the development of psychiatric illnesses.[21] The progression in treatment, from the use of precursors to the reuptake inhibitors has paralleled our understanding of the serotonin system.[22] The latest advances in treatment, the use of receptor specific agents is the next logical refinement in our progress towards a clearer, more rational basis for treatment of patients with psychiatric illness.

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