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EDITORIAL

Serotonergic mechanisms and the new antidepressants[1]

The renaissance in serotonin pharmacology of the past decade is resulting in the discovery of a vast array of new medications now undergoing human testing and which are expected to burst forth into psychiatry over the next decade. This proliferation of new drug therapies is the result of advances in the basic neuroscience of serotonin being translated into clinical applications. The challenge now is to develop the opportunities presented by the new knowledge of serotonin pharmacology to gain a greater understanding not only of depression and antidepressants, but also to extend such advances to treatments in uncharted areas while being vigilant for unexpected adverse drug reactions.

SEROTONIN *VERSUS* NOREPINEPHRINE REUPTAKE BLOCKADE

For decades, it has been known that the classical tricyclic antidepressants blocked – to a greater or lesser extent – the synaptic reuptake of both serotonin and norepinephrine (Enna *et al.* 1981). Debates raged in the 1970s about whether there were 'serotonin depressions' in some patients *versus* 'norepinephrine depressions' in others, such that selective agents might be useful in one group but not the other (Feighner & Boyer, 1991). There was theoretical concern at the time when highly selective agents were first being developed in research laboratories that selective agents would actually prove to be less useful than non-selective agents. Opposing this point of view was the possibility that selective agents would have a favourable side effect profile as well as greater potency, thus allowing a greater degree of reuptake blockade.

Today, clinical experience is accumulating at a rapid pace for a group of agents referred to as 'serotonin selective reuptake inhibitors' (SSRI) or 'serotonin uptake inhibitors' (SUI). These are listed in Table 1. The data to date suggest that SSRIs are not only generally comparable in efficacy to the 'non-selective' blockers of old for the treatment of depression, but SSRIs have a generally more favourable side effect profile plus indications of efficacy in additional psychiatric disorders such as obsessive compulsive disorder (Feighner & Boyer, 1991). Indeed, the number of psychiatric disorders with putative links to serotonin and which are undergoing testing with SSRIs is very large (see Table 2).The modulatory role of serotonin in a wide range of behaviours is only beginning to

Table 1. *Serotonin selective reuptake inhibitors*

Fluoxetine
Fluvoxamine
Sertraline
Paroxetine
Citalopram

Table 2. *Potential therapeutic applications for serotonergic agents*

Obsessive compulsive disorder
Panic disorder
Social phobia
Suicidal ideation
Impulse control disorders
Substance abuse
Eating disorders
Personality disorders
Violence
Mixed anxiety depression

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be understood, and its role in depression seems now to be just one of its many potential roles (see Table 2). Some of the novel therapeutic uses for SSRIs are the unique product of the serotonin (*versus* norepinephrine) selectivity of these agents (e.g. obsessive compulsive disorder), whereas other novel therapeutic uses may be more the product of careful study of new disorders rather than anything linked to serotonin selectivity itself (e.g. panic disorder). Where the applications of SSRIs will extend, and when we will meet the limits of their therapeutic utility in psychiatry are unclear, but it is certain that the launch of this new class of agents as antidepressants is merely the first volley from an ultimate clinical armamentarium.

ADVERSE EXPERIENCES: SUICIDE AND VIOLENCE?

A recent episode in the United States involving one of the SSRIs underscores the difficulty of studying rare events in psychiatry. Case reports associating suicidal ideation and treatment with the SSRI fluoxetine (e.g. Teicher *et al.* 1990) were ultimately sensationalized by the media, with misinformation being the order of the day. Both pre-clinical and clinical data have long linked serotonin with impulsive, violent and suicidal behaviour, giving a potentially credible scientific foundation to the possibility that SSRIs could alter such behaviours. For example, a relationship has been shown between low cerebrospinal fluid levels of the serotonin metabolite 5-HIAA (5-hydroxyindole acetic acid), suicidal behaviour and aggression among patients with depression (e.g. Åsberg *et al.* 1987; Roy & Linnoila, 1990). Significant negative correlations have also been reported for cerebrospinal fluid 5-HIAA and impulsive violent behaviour among murderers, attempted murderers and arsonists (Brown *et al.* 1979; Virkkunen *et al.* 1987).

Another important piece of background information was the association of a prior SSRI, zimelidine, with a serious adverse reaction (drug fever and Guillain-Barré syndrome), resulting in its withdrawal from world-wide markets, creating nervous anticipation of potential problems from this class of drugs by physicians (Fagius *et al.* 1985). Although there have been to date no published reports of Guillain-Barré syndrome with any of the SSRIs listed in Table 1, there have been anecdotal reports linking fluoxetine with everything from suicidal ideation in depressed patients to testimonials from murderers seeking exculpation. Such reports have confused and frightened both physicians and patients.

Data have recently been analysed looking for an association between fluoxetine treatment and increases in suicidal and violent behaviour, but no evidence has yet been found proving any such association (Beasley *et al.* 1991). While clinicians must remain vigilant to unexpected and rare adverse experiences with all new drugs, anecdotal reports must ultimately be confirmed by epidemiological analyses in large data bases before any chance observations can be inferred to have a cause and effect relationship.

SEROTONIN RECEPTOR SUBTYPES

A major paradox has evolved since the discovery of the SSRIs. That is, recent advances in the neuroscience of serotonin have demonstrated such a multiplicity of serotonin receptor subtypes, that the term 'serotonin selective' is now virtually obsolete. Although the group of SSRIs are indeed selective for serotonin reuptake over norepinephrine reuptake, SSRIs act non-selectively at all of the multiple serotonin receptor subtypes. That is, SSRIs generally enhance serotonin itself, and by doing so, cause all of the many serotonin receptor subtypes to be stimulated by serotonin. True serotonin selectivity, it seems, has now been redefined by the selective agonists and antagonists for each of the various serotonin receptor subtypes, and can now be attained for key individual serotonin receptor subtypes with even newer agents, but not with the SSRIs. A listing of the multiple serotonin receptor subtypes is given in Table 3.

As demonstrated in Table 3, a multiplicity of unique receptors has been identified in addition to the serotonin reuptake site on the presynaptic axon terminal (Martin, 1990). All of these receptors interact with serotonin itself. These receptors are located on various sites of the serotonin neuron

Table 3. *Serotonin receptor subtypes*

1A	1B/1D	2/1C	3/4
Somatodendritic	Presynaptic	Postsynaptic	Postsynaptic
Autoreceptor	Autoreceptor	Choroid plexus	Ion channel
Postsynaptic	Vascular	Phosphatidylinositol	Emesis
Adenylate cyclase	Migraine	Depression	Ondansetron
Azapirones (buspirone)	Sumatriptan	Obsessive compulsive disorder	
Anxiety/depression			

(e.g. raphe cell bodies or presynaptic axon terminals) as well as postsynaptically on other neurons. Serotonin receptor subtypes are expressed by different genes, and several of these genes have now been cloned (Hartig *et al.* 1990). Different receptor subtypes have differing second messengers linked to them, and of course each receptor subtype has unique agonists and antagonists which interact selectively with it (Hartig *et al.* 1990; Martin, 1990).

Even the older antidepressants in retrospect are now known to have actions on serotonin sites other than the classical reuptake site. For example, trazodone, amitriptyline and mianserin all have some degree of $5HT_2$ antagonist properties (Leysen, 1990). Agonists and antagonists for each of the various serotonin receptor subtypes are known and are in clinical testing for multiple psychiatric disorders, including depression. Thus, agonists for the 1A subtype of serotonin receptor, many of which come from the azapirone class of compounds, are being tested in generalized anxiety disorder, in major depressive disorder, and in mixed anxiety depression (Stahl *et al.* 1992). Selective antagonists for the serotonin-2 receptor are being tested as novel treatments for schizophrenia, for anxiety and for dysthymia/chronic depression (Grahame-Smith, 1992). Serotonin-3 antagonists hold promise as antipsychotics and as anxiolytics (Grahame-Smith, 1992). The serotonin-2 and -3 antagonists have entirely unique behavioural pharmacology profiles from other therapeutic agents in psychiatry, and an entirely different side effect profile, suggesting novel therapeutic applications as well as better tolerability.

NOVEL PSYCHOPHARMACOLOGY: PARTIAL AGONISTS

Another novel pre-clinical concept arising from basic neuroscience discoveries in serotonin research is that of partial agonists, particularly for the serotonin 1A receptor. This concept is, of course, generally applicable throughout all areas of pharmacology, but in its application to serotonin, has played out as the development of a series of azapirone serotonin 1A agonists, which are quite comparable in their pharmacological potency and selectivity, but which differ among themselves essentially as a potency series of how partial or how full they are (Stahl, 1992). That is, at one end of the spectrum is a full agonist, which elicits the same degree of physiological receptor-mediated response as serotonin itself; at the other end of the spectrum is a full antagonist which blocks the effects of agonists, but has no agonist properties itself.

What is so interesting about partial agonists, is that they can appear as net agonists, or as net antagonists, depending upon the amount of endogenous serotonin present. Thus, in the absence of serotonin, the partial agonist is a net agonist. In the presence of serotonin, the partial agonist is a net antagonist. Thus, the partial agonist will theoretically boost deficient serotonergic activity and reduce excessive serotonergic activity.

An agonist and an antagonist in the same molecule is quite a new dimension to therapeutics. This has led to proposals that serotonin 1A partial agonists could treat not only states which are theoretically deficient in serotonin (such as depression), but also states that are theoretically in excess of serotonin (such as anxiety) (Eisen, 1980; Stahl, 1992; Stahl *et al.* 1992). Indeed, as mentioned above, these serotonin 1A partial agonists are looking quite promising for the treatment both of generalized anxiety disorder as well as major depressive disorder (Stahl *et al.* 1992). What

is not yet known is what degree of partiality is optimal. The potency series now in clinical testing should be yielding this answer in due course.

NEW CLINICAL USES FOR NOVEL AGENTS AT SPECIFIC SEROTONIN RECEPTORS

Development of new therapies for psychiatric disorders is greatly hampered by the lack of knowledge of the molecular lesions or even the biochemical pathophysiologies of psychiatric disorders. In the absence of this information, rational use of the new serotonergic agents is limited to relatively empirical testing. However, the background of the past 40 years of research links both pre-clinical and clinical observations to serotonergic functioning in a wide range of behaviours and disorders of behaviour. Thus, hypothesis-orientated and theory-driven testing of the new therapeutic tools for serotonergic receptor subtypes is possible and is indeed proceeding at a very fast pace (Stahl, 1992). Just as the SSRIs are being utilized as therapeutic tools in a wide range of psychiatric symptoms and disorders, so is the plethora of agonists, antagonists and partial agonists for each of the serotonin receptor subtypes.

The opportunities for hypothesis-orientated testing by clinical psychopharmacologists are stunning, and without precedent. Selective agents are cascading into clinical testing which now targets the different receptors for the serotonin system, and it is now possible to use these agents as tools to alter behaviours in disorders where independent information suggests that modulation of that receptor might have useful therapeutic actions. Such an approach amounts to a pragmatic and opportunistic use of selective pharmacological agents in a theory-driven context of psychiatric disorders based upon evidence linking that disorder to serotonin. However, this link to serotonin at the present time is often theoretical or based upon extrapolations from pre-clinical studies, and far from an established molecular lesion or proof that the hypothesized link is related to the primary lesion for the disorder (Stahl, 1992). Such biologically empirical studies proceed without prior assurance that this approach will necessarily be useful therapeutically since one is not providing a likely and rational pharmacological compensation for a known deficit.

Despite the limitations of this approach, it has been the manner in which innovations in psychopharmacology have historically occurred, and it has produced the empirical breakthroughs which have led to those treatments for psychiatric disorders which are present today. There is perhaps no better current example than serotonin in psychiatry where discoveries in basic neuroscience are leading to innovations in clinical science and drug development. It should be an exciting decade ahead of us.

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