EDITORIAL

Serotonin in Psychiatric and Behavioral Disorders

The Role of SSRI

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Serotonin (5HT) is an indolamine with a wide distribution in plants, animals and man. In mammals, it is found in blood platelets, mast cells and the enterochromaffin cells of the gut. Numerous studies have shown that the serotonergic projection to the forebrain arises from the cell bodies within the raphe nuclei of the rostral brain stem, principally, the dorsal and median raphe nuclei. The rostral part of the dorsal rap he projects to the striatum and cortex, while the caudal portions along with neurons in the median rap he projects to the hippocampus and limbic systems (*Fuxe et al., 1968*). The levels of 5 HT in the CNS only represents about 1-2% of the total amount found in the body (*Bradley, 1989*). The indolamine cannot cross the blood brain barrier and hence all the neuronal 5HT in the CNS is synthesized locally.

Serotonin is formed by a two-step process involving the hydroxylation of the essential amino acid L-Tryptophane to 5-hydroxytryptophane (5HT). L-Tryptophane crosses the BBB and neuronal barrier using a competitive facilitated carrier for neutral amino acids.

Human behavior and behavioral disorders are psychobiologically complex and the most variable models for neuropsychiatric disorders are based on psychobiologic and biological interactions occurring over the life span of individuals. For decades it has been known that the classical TCA blocked to a greater or lesser extent the synaptic re-uptake of both 5-HT and Norepinephrine. Debates raged in the 1970's about whether there was "Serotonin depression" in some patients versus "Norepinephrine depression" in others, such that selective agents can be used in one group and not the other, but this has not proved to be true.

Selective agents would have a favorable side-effect profile, as well as greater potency thus allowing a greater degree of re-uptake blockade. Clinical experience is accumulating at a rapid pace for a group of agents referred to as Serotonin Selective Re-uptake Inhibitors (SSRI) Serotonin Uptake Inhibitors (SUI). The available list of these are: Fluoxetine, Fluvoxamine, Sertraline, Paroxetine and Citalopram.

The data to date suggest that SSRI's are not only generally comparable in efficacy to the non-selective blockers of old TCA's for the treatment of depression, but SSRI's generally are a more favorable side effects profile plus indicators of efficacy in additional psychiatric disorders. The number of psychiatric disorders which can be related to Serotonin metabolism and can be helped by the SSRI's are as follows:

Depression
OCD
Anxiety and panic attacks
Social phobia
Suicidal ideation
Impulse control disorder e.g. trichotillomania, pathological gambling
Substance use disorder e.g. alcoholism
Eating disorders, e.g. bulimia
Personality disorder with impulsive traits
Violence
Mixed anxiety-Depression
OCD related disorders e.g. Basal ganglia syndromes, Tourette syndrome Paraphillas.

This is apart from the fact that Serotonin plays a major role in other behavioral aspects like pain, temperature and sleep.

Both preclinical and clinical data have long linked Serotonin with impulsive, violent and suicidal behavior, giving a potentially credible scientific foundation for the possibility that SSRI could alter such behaviors. A relationship has been shown between low CSF level of Serotonin metabolite 5 hydroxyindolacetic acid (HIAA) in suicidal patients and aggression among patients with depression. Significant negative correlates have also been reported for CSF-5-HIAA and impulsive violent behaviour among murderers, attempted murderers and arsonists (*Stahl, 1993*).

In contrast to panic disorder, patients' therapeutic responses in OCD are highly restricted to drugs that are 5HT selective uptake inhibitors like Clomipramine, Fluvoxamine, Fluoxetine and Citalopram. Patients with

panic disorder respond not only to these drugs, but also to a broad spectrum of agents including Norepinephrine selective and non-selective uptake inhibitors. MAOI and long acting BZ. TCA were found to inhibit the catabolism of the re-uptake of monoamine neurotransmitters (NA, 5HT, DA) released at synapses in the brain.

Further research focused on Serotonin receptors. The term "selective" is now virtually obsolete. SSRI's act not selectively at all on the multiple Serotonin receptor subtypes. True, 5-HT selectivity, it seems, has now been redefined by the selective agonists and antagonists for each of the various Serotonin receptor subtype, with even newer agents but not with the SSRI's (*Stahl, 1993*).

Contrasting results are available from a more limited data base which suggest that panic episodes in panic disorder patients can be provoked by a number of different chemical agents including Na lactate, Yohimbine, Caffeine, Phenfluramine and M-CPP. On the other hand, OCD symptoms exacerbations have been reported to develop in OCD patients only during treatment with 5-HT agonists like M-CPP and not during treatment with other anxiogenic agents that have been studied. Many 5-HT-dopamine and 5-HT-neuropeptide interactions have been well documented with panic disorder. Some hypotheses suggest that 5-HT may be involved only in an intermediary fashion in the genesis of anxiety. Within the brain 5-HT pathways, there appear to be multiple subsystems that utilize over 6 different 5-HT subtypes. These 5-HT subsystems act independently potentiating or opposing one another.

Serotonin receptor subtypes are expressed by different genes. Several of these have now been cloned. Even the old antidepressants, in retrospect, are known to have actions on Serotonin sites other than the classical re-uptake sites. For instance Trazodone (*Trittico*), Amitryptilene (*Tryptizol*) and Mianserin (*Bolvidon*) all have some degree of 5-HT2 antagonist properties. The Azapirones (*Buspirone*) are 5-HT partial agonists. At low doses they compete with Serotonin at neurotransmitter sites to decrease anxiety. At higher doses the Azapirones are direct agonists and thus antidepressants. Agonists of the 5-HT 1A subtype, many of which come from the Azapirone group of compounds, are being tested in GAD, major depression and mixed anxiety depression. Selective 5-HT2 receptor antagonists are being tested as novel treatment for schizophrenia, anxiety, dysthymia and chronic depression. The Serotonin 2 and 3 antagonists have an entirely unique behavioural pharmacological profile compared to other therapeutic agents in psychiatry, and an entirely different side-effect profile suggesting novel therapeutic applications as well as better tolerability (*Stahl. 1993).*

The Serotonin 1A agonists which are quite comparable in their pharmacological potency and selectivity differ among themselves essentially as a potency series of how partial or how full they are. At one end of the spectrum, they are full agonists which elicit the same degree of physiological receptor. At the other end of the spectrum, they are full antagonists, which block the effects of agonists, but have no agonist properties themselves. They can appear as net agonists or net antagonists according to the amount of endogenous Serotonin present. In the absence of Serotonin, the partial agonist is a net agonist. In the presence of Serotonin, the partial agonist is a net antagonist. The partial agonist will theoretically boost the deficient Serotonin activity and reduce excessive Serotonin activity. This has led to the proposal that 5HTIA partial agonists could treat not only states which are theoretically deficient in Serotonin as depression but all states that are in excess of Serotonin as anxiety.

The SSRI's Paroxetine, Citalopram, Fluoxetine, Fluvoxamine and Sertraline constitute a structurally diverse group of drugs which vary in their relative potency and selectivity for the neuronal Serotonin re-uptake mechanism. Paroxetine is the most potent drug in this class in vitro and after oral administration. Whereas Citalopram exhibits the greatest selectivity of inhibition of Serotonin re-uptake relative to that of catecholamine re-uptake. In contrast to Paroxitine and Fluvoxamine, Citalopram, Fluoxetine and Sertraline are metabolized in vivo to products that possess similar pharmacological properties to those of the parent molecule. Interestingly, although sertraline, Fluoxetine and Fluvoxamine all to the same extent down-regulate central beta adrenoceptors, no effects have been observed with the more potent and selective representative of this class Paroxetine and Citalopram. This provides further support to the hypotheses that the down regulation of central beta adrenoceptors in animals is not predictive of antidepressant properties in man.

However, more constant effects are observed with these drugs on the dopaminergic system. Paroxetine, Fluoxetine and particularly Citalopram have been reported to increase the sensitivity of the mesolimbic dopaminergic mechanism after repeated administration. This effect has also been demonstrated by the TCA. Citalopram also reduces the binding of the specific ligand to D1 sites on repeated administration. The SSRI's do not induce marked changes in animal behaviour, although activation of the EEG and suppression of REM sleep are also consistent findings in animals. It may seem contradictory to argue that a

serotonergic hypothesis of depression is incomplete and then state that drugs that inhibit Serotonin re-uptake are very important as antidepressants. However, we may argue that the importance of the SSRI's at present lies in clinical rather than chemical properties. Such clinical properties include efficacy in depression, OCD, panic and OCD-related disorders etc., coupled with a relative lack of side-effects and toxicity in overdose (*Feighner and Boyer, 1991*).

Drug Interactions Several reports have appeared on the development of increased TCA plasma levels when a TCA is administered with an SSRI. But we have treated a number of patients with a combination of SSRI and TCA and have not seen any unusual degree of adverse effects. Also there have been reports of significant negative interaction between SSRI and Lithium including the development of mania. Again, this combination has been used successfully by many authors in a number of patients during the depressive phase of a bipolar illness and in patients with refractory unipolar depression (*Pope et al., 1988*).

The most serious drug interaction occurs when SSRI's are given in combination with MAOI's, where the "Serotonergic syndrome" may occur. It is characterized by myoclonus, hypertension, changes in mental status especially confusion, hypomanic symptoms such as pressure of speech, hyperactivity, irritability and euphoria. There may be also diarrhea with abdominal cramping, tremors, tachycardia and elevated temperature. In severe cases hyperpyrexia, cardiovascular collapse and death may occur (*Sternbach, 1988; Brasseur, 1989; Feighner et al., 1990*).

The SSRI's have been compared with the TCA in a large number of controlled trials in depression. In the majority of these, there were no significant differences between the two treatments. In a few studies, either TCA or SSRI were significantly superior. The only difference was the selection of patients and profile of side-effects. There is also some evidence that SSRI have demonstrated their efficacy in atypical depression or in depression with some prominent symptoms such as panic, eating disorder or OCD. SSRI's have demonstrated their efficacy in the treatment of panic disorder, OCD and mixed Anxiety-Depression. Their usefulness has emphasized the importance of the Serotonin system in the etiology of these disorders.

The SSRI's offer the clinical advantage of providing symptomatic relief for these indications without the anticholinergic, antihistaminic and cardiovascular side-effects or weight gain associated with the TCA. The efficacy of SSRI versus TCA and MAOI for these indications is also a field for further research and study.

Other Potential Indications of SSRI'S

1. A large number of studies have indicated that suicidal ideation and attempts are linked to 5-HT dysfunction. Several studies have found Citalopram, Fluoxetine and Fluvoxamine to be more effective than TCA in reducing suicidal ideation. Conversely, drugs that inhibit the intake of NA may be associated with an increased risk of suicide compared to placebo (*Muijen et al., 1988; Mullin et al., 1988; Wakelin, 1988; Gazner, 1989; Montgomery, 1989*).

2. Alcoholism may also be tied to dysfunction of the serotonergic system. The evidence for this comes from several sources. Serotonin depletion enhances alcohol consumption in animals, and recent studies of 5-HT1A agonists such as Buspirone suggest the efficacy in reducing craving for alcohol. Lithium which may work through serotonergic mechanisms has also been reported to aid abstinence in alcoholics. Several studies have shown that SSRI have reduced alcohol consumption in animal and man. Also, data from animal studies suggest that SSRI may also be helpful in the treatment of stimulant abuse like Amphetamine (*Gorelick, 1989*).

3. Eating disorders bear some similarities to substance use disorder. Serotonin may be involved here. Serotonin regulates satiety; so low Serotonin activity causes overeating in animals, and may be linked to obesity in man. Anorexia is associated with an increase in the function of Serotonin. Clinical use of SSRI may be associated with loss of appetite and weight (*Angel et al., 1988*). This effect is generally proportional to the potency in blocking the re-uptake of 5-HT dysfunction. It was suggested that binging and vomiting may change the ratio of plasma amino acids, which in turn enhances Serotonin mediated satiety in the brain and/or may result in improvement of the mood. This hypothesis was based on data showing that the intake of dietary carbohydrates increase the brain uptake of Tryptophane by increasing the plasma ratio of Tryptophane to other amino acids that compete for uptake in the brain.

4. Again, Serotonin activity correlates with some aspects of personality. The characteristics of impulsivity, anger, anxiety, poor anxiety tolerance and violence and loss of control are most closely associated with the cluster B of the DSM-III personality disorders, which is so-called dramatic, emotional and erratic (*Comelius et al., 1989*). This includes the border-line, histrionic, narcissistic and antisocial personality disorders. There is also a frequent overlap of these disorders with other conditions that respond to SSRI's such as panic disorder, alcoholism, bulimia and impulsive suicidal behaviour. Data on the beneficial use of SSRI's in patients with personality

disorders are, therefore, interesting. Cluster C of DSM-III personality disorders is also known as the anxious, fearful cluster, because anxiety is a common feature of these disorders. Because of the beneficial effects of the SSRIs in Axis I Anxiety disorder, patients with one of these related axis II disorders may also improve.

5. Other uses of SSRI's in neurological disorders include reports of some benefit in pseudobulbar palsy (*Come and Hall, 1989*), crying spells following stroke, depression following severe head injury (*Cassidy, 1989*), in cataplexy and narcolepsy (*Schachter and Parkes, 1980; Langdon et al., 1986*). It may improve the memory function in the treatment of dementing disorders. In man both Citalopram and Fluvoxamine have been helpful in alcohol related and other dementias (*Nyth et al. 1989: Martin et al., 1989*). Citalopram was helpful in decreasing emotional symptoms in patients with senile dementia of the Alzheimer's type, but not in patients with vascular dementia. Pain is another area in which SSRI may make a contribution, but relatively few studies have been reported. The SSRI's have analgesic effects in laboratory animals, may be related to their effects on endogenous opioids and also of increasing the level of plasma beta endorphins and beta lipotrophins. There have also been some reports on their effect on painful diabetic neuropathy and the treatment of headache and fibrositis (*Theesen and Marsh, 1989*).

SSRI's are very effective in OCD as a disorder which was resistant to previous TCA. OCD as mentioned before is associated with low Serotonin turnover.

The side-effect profile is perhaps the most important area in which SSRI differs from earlier antidepressants. The rate of compliance and of drop-outs from clinical studies on SSRI's as compared to other groups of antidepressants is very low. As mentioned before, compared to the TCA, there are minimal or low cardiovascular effects, anticholinergic effects, no gross sedative effects and no effect on weight. There might be, however, some gastrointestinal effects early in the treatment in the form of nausea and vomiting. Also CNS effects may appear in some cases in the form of some anxiety, nervousness, racing thoughts, tremors, insomnia and vomiting. Anorgasmia, arthralgia and rash are very rare complications. An early SSRI Zimelidine was withdrawn because of serious hypersensitivity reactions mainly in the form of Guillan Barre Syndrome (*Stahl, 1993*). Fortunately, this does not appear to be a property of SSRI's in general and has not been reported with other drugs in this class. Suicidal attempts with SSRI's were almost safe as compared to the same dosage of other antidepressant drugs. Currently, there are no published studies which compare one SSRI to another, but these are underway. In countries where more than one SSRI is available, the trials between them must be made on clinical grounds. One should remember that most practitioners feel that there are significant clinical differences between the TCA, even though chemical structures differ very little. The chemical structures of the SSRI's are very different from each other. However, this suggests that there may be even greater differences. Experience with these compounds points to some meaningful distinguishing points: the very long half-life of Fluoxetine and its metabolite Norfluoxetine, made it possible to treat patients every few days. Although this may be an advantage for patients who are unable to comply with a regular treatment regimen, it may lead to side-effects being more prolonged. When selecting an antidepressant, it is a good practice to have an alternative in mind if the first drug is ineffective. If a MAOI is a future option, it would be best to choose an SSRI with a relatively short half-life as this will minimize the wash out period before a switch is made to the MAOI. The side-effect profile between the different SSRI's are likely to differ, somnolence may be more common with Fluvoxamine and Paroxetine than with Fluoxetine, Sertraline or Citalopram. We have also observed a higher frequency of nausea with Fluvoxamine and lower incidence of weight loss with Paroxetine. Since minimum effective doses have not been established for most of these drugs, it is possible that some of these clinical differences are dose dependent.

Most comparative studies indicate that SSRI's begin to exert a therapeutic effect at about the same time as TCA. However, the response may sometimes be delayed to 6 weeks or more.

Combination treatment In resistant cases, a combination of SSRI and a TCA can be helpful. Again the adjunctive use of Lithium with an SSRI may be advantageous in some depressed patients resistant to the other antidepressants (*Weilburg et al., 1989*). Other reports claim good results in resistant cases of the combination of the SSRI with amphetamine or with the thyroid hormone. As mentioned before with Panic disorder, we can use the BZD like Alprazolam or Clonazepam, MAOI, TCA and recently the initiation of treatment with an SSRI has obtained encouraging results.

In OCD patients, combination treatment with other medications may sometimes be helpful. Buspirone at a dose of about 30 mg/day was added to the SSRI in patients who did not fully respond to 10 days of treatment. This produced further improvement (*Markovitz et al.,1989*). Also the addition of Trazodone was effective (*Swerdlow and Andia, 1989*). Sometimes the addition of neuroleptics or of phenfluramine can

change a resistant OCD into a responsive one (*McDougle et al.,1989*).

Development of new therapies in psychiatric disorders is greatly hampered by the lack of knowledge of the molecular lesions or even the biochemical pathophysiology of psychiatric disorders. Hypothesis-oriented and theory-driven testing of the new therapeutic tools for Serotonergic receptor subtypes is, indeed, proceeding at a very fast pace. The SSRI's 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 (*Stahl, 1993*).

References

Angel I; Tauranger MA; Claustre Y et al. (1988): Anorectic activities of Serotonin uptake inhibitors: correlation with their potencies at inhibiting Serotonin uptake in vivo and 3H-mazindol binding in vitro. Life Sci 43, 651-658.

Bradley PB (1989): Introduction to Neuropharmacolgy, p.351 Butterworth and Co.

Brasseur R (1989): A multicenter open trial of Fluoxetine in depressed outpatients in Belgium. Int. Clin. Psychopharmacol. 4 (suppl 1), I07-1 111.

Cassidy JW (1989): Fluoxetine: a new serotonergically active antidepressant. Special issue: visual system dysfunction. Journal of Head Trauma Rehabilitation 4, 67-69.

Corne SJ and Hall, JR (1989): A double blind comparative study of Fluoxetine and Dothiepin in the treatment of depression in general practice. Int. Clin. Psychopharmacol 4,245-254

Cornelius JR; Soloff PH; Perel HM et al (1989): Fluoxetine trial in borderline personality. New research program and Abstracts. American Psychiatric Association 142nd Annual Meeting P.192.

Feighner JP; Boyer WF; Tyler D et al (1990): Fluoxetine and MAOI'S: Adverse interactions. J. Clin. Psychiatry

Feighner JP; Boyer WF (eds.) (1991): Selective Serotonin re-uptake inhibitors, perspective in Psychiatry, Vol. I John Wiley and Sons.

Fuxe K; Hoekfelt T; and Ungerstedt U. (1968): Localization of Indolamines in the CNS Adv Pharmaco; 6, 235-251.

Gazner P (1989): Fluvoxamine therapy for the depressed patients. In Stefanis CN, Soldateos CR and Rabavilas AD (eds.) Psychiatry Today: VIII World Congress of Psychiatry Abstracts, p. 55 .New York Elsevier.

Gorelick DA (1989): Serotonin uptake blockers and the treatment of alcoholism. Recent Dev. Alcohol 7, 267-281.

LangdonN; Shindler J; Parkes JD. et al (1986): Fluoxetine in the treatment of cataplexy. Sleep 9, 371-373.

Markovitz PJ; Stagno SJ and Calabrese JR (1989): Buspirone augmentation of Fluoxetine in obsessive and compulsive disorder. Biol. Psychiatry 25 (Suppl 7A), 186A.

Martin PR; Adinoff B; Eckhardt MJ et al. (1989): Effective pharmacotherapy of alcoholic amnestic disorder with Fluvoxamine. Arch. Gen. Psychiatry 46, 617-624.

McDougle CJ; Goodman WK; Price LH et al. (1989): Neuroleptic addition in Fluvoxamine refractory OCD . New Research Program and Abstracts, American Psychiatric Association 142nd Annual Meeting p. 189.

Montgomery SA (1989): 5-HT re-uptake inhibitors in the treatment of depression . In: Montgomery SA (ed.) Citalopram: the New Antidepressant from Lundbeck Research pp. 1-10. Amesterdam: Excerpta medica.

Muijen M; Roy D; Silverstone T et al (1989): A comparative clinical trial of Fluoxetine Mianserin and Placebo in depressed outpatients. Acta. Psychiatry Scand. 78, 384-390.

Mullin JM; Pandita Gunawaradena VR and Whitehead AM (1988): A double blind comparison of Fluvoxamine and Dothiepin in the treatment of major affective-disorders.Br. J. Clin. Pract. 42, 51-55.

Nyth A.L., Gottfries CG, Elgen K, et al (1989): The clinical efficacy of citalopram in treatment of emotional disturbances in dementia disorders. In Stefanis CN, Soldatos CR and Rabavilas AD, (eds.) Psychiatry Today: VIII World Congress of Psychiatry Abstracts, p. 503 New York: Elsevier.

Overo K.F. (1989): The pharmacokinetic and safety evaluation of Citalopram from preclinical and clinical data. In: Montgomery Sa (ed.) Citalopram: the New Antidepressant from Lundbeck Research, pp. 22-30. Amesterdam: Excerpta Medica.

Overo K.F: Toft B. Christophersen L et al. (1985): Kinetics of citalopram in elderly patients Psychopharmacology 86, 253-257.

Pope HG JR; McElroy SL and Nixon RA (1988): Possible synergism between Fluoxetine and Lithium in refractory depression. Am. J. psychiatry, 145, 1292-1294.

Schachter M. and Parkes J.D. (1980): Fluvoxamine and Clomipramine in the treatment of cataplexy. J. Neurol Neurosurg. Psychiatry 43, 171-174.

Stahl S.M. (1993): Serotonergic Mechanisms and the new antidepressants. Psychological Medicine, 23, 281-285.

Sternbach H (1988): Danger of MAOI therapy after Fluoxetine withdrawal. Lancet II 850-851.

Swerdlow N.R. and Andia AM. (1989): Trazodone-Fluoxetine combination for treatment of obsessive-compulsive disorder (letter) Am. J. Psychiatry 146, 1637.

Theesen KA and Marsh WR (1989): Relief of diabetic neuropathy with fluoxetine. DICP 23, 572-574.

Wakelin JS (1988): The role of Serotonin in depression and suicide: Do Serotonin re-uptake inhibitors provide a key. In: Gastpar M and Wakelin JS (eds.) Selective 5-HT re-uptake inhibitors: Novel or commonplace agonists. pp 70-83. Basel: Karger.

Weilburg JB; Rosenbaum JF; Biederman J. et al. (1989): Fluoxetine added to non-MAOI antidepressants converts non-responders: a preliminary report. J. Clin. Psychiatry 50 447-449.

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