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S17. Selective Serotonin Reuptake Inhibitors as broad-spectrum therapeutic agents

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PRE- AND POST-SYNAPTIC MECHANISMS AFTER LONG-TERM ADMINISTRATION OF SSRIs

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cAMP dependent protein kinase (cAMP PK) is a central component of cAMP signalling, since with very few exception all known cAMP dependent effects within the cell are mediated through the activation of the enzyme. In the absence of cAMP, the enzyme exists as an inactive tetrameric complex, composed of two catalytic (C) and a regulatory (R) subunit dimer which represents the receptor for cAMP. Activation occurs by cAMP binding to regulatory subunits, which promotes dissociation of the complex and the release of the free and active catalytic subunits. Once released from the holoenzyme state, C moieties are able to phosphorylate specific substrate proteins which in turn regulate a variety of cellular functions such as receptor desensitization, ion channel sensitivity, cytoskeleton organization and gene expression.

The regulation of cAMP receptors represents a fundamental step in signal transduction and a possible target for drugs that modify neurotransmission such as antidepressants. We have shown that 10 days of treatment with desmetylimipramine (DMI) a tricyclic antidepressant (TCA) increased the amount of a protein band in rat cerebral cortex that for its biochemical properties appears to be the R subunit of cAMP PK. Further characterization of this result was obtained by a combination of SDS–PAGE photoaffinity labeling with $8N_3$ [^{32}P]cAMP and autoradiography. DMI given for 10 days enhanced the covalent binding of ^{32}PcAMP to R subunit in the soluble fraction of rat cerebral cortex. Moreover, we have demonstrated that different antidepressants such as (+) oxaprotiline which specifically blocks norepinephrine uptake, and fluoxetine, paroxetine and fluvoxamine, which are specific serotonin reuptake inhibitors (SSRI) were also able to affect the cAMP phosphorylation system.

Recent evidence obtained in our laboratory indicates that at least in rat cerebral cortex, cAMP PK type II is associated with microtubules through the binding of R subunits to specific microtubules associated proteins. These findings suggest that within the cell microtubules could play an important role in the modulation of the intracellular signal transduction processes.

Interestingly, DMI and SSRIs were able to increase the covalent binding of ^{32}P cAMP into 52 KDa cAMP receptor associated with rat cerebrocortical microtubule fraction.

We are now investigating the effects of SSRIs and TCAs on the phosphorylation of presynaptic proteins which are important in regulating the release of neurotransmitter.

In conclusion these results strongly suggest that cAMP protein kinase could be an intracellular target for the action of antidepressant drugs.

AFFECTIVE SPECTRUM DISORDER: A FAMILY OF DISORDERS SHARING RESPONSE TO ANTIDEPRESSANTS

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Response to pharmacologic treatments may identify groups of disorders with a common pathophysiology. Applying a treatment response model based on four classes of antidepressants (tricyclics types, monoamine oxidase inhibitors, serotonin uptake inhibitors, and atypical agents) to the medical literature, Hudson and Pope (1990) identified eight disorders that have been shown to respond to antidepressant drugs from at least three of these four classes with efficacy in placebo-controlled studies established in at least one. These disorders include: major depression, bulimia, panic disorder, obsessive-compulsive disorder, attention-deficit hyperactivity disorder, cataplexy, migraine, and irritable bowel syndrome. Hudson and Pope suggested that disorders might share a common pathophysiologic abnormality and comprise a larger family which they termed affective spectrum disorder. Recently, we have extended this framework to include other disorders that have been shown to respond to antidepressants. These include binge eating disorder, the impulse control disorders, and body dysmorphic disorder. That many of these conditions share abnormalities in compulsivity and/or impulsivity as well as response to antidepressants has led to the speculation that they may be members of a family of compulsive-impulsive disorders, which, in turn, belongs to the larger family of affective spectrum disorder. Treatment response, phenomenologic, and family studies supporting this conceptualization will be reviewed, with special emphasis on bulimia nervosa, binge eating disorder, body dysmorphic disorder, the impulse control disorders, and attention-deficit hyperactivity disorder.

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DEPRESSIVE DISORDERS: CORRELATING SEVERITY AND TREATMENT

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The development of SSRIs, such as fluoxetine, advance the treatment of depressive illness in a number of ways. Firstly, they provide us with drugs which can be commenced at the therapeutic dose, unlike tricyclic antidepressants which are commenced at a sub-therapeutic dose which needs to be progressively escalated. Secondly, they are a well tolerated group of compounds which do not add to the burden of symptoms already experienced by the depressed patient. Thirdly, in comparison to the tricyclic antidepressants they are safe when taken in overdose. In the past it has generally been accepted that for a drug to have an action on the anxiety component of depression it must be sedative. The SSRIs are clearly an exception to this rule. Fluoxetine, for example, dramatically reduces scores on the anxiety variables in the Hamilton Depression Rating Scale without having a sedative action. The same is true in relation to the sleep disturbance seen in depressive illness. SSRIs over a period of 1-2 weeks normalise sleep architecture despite the fact that they do not induce sedation. For a depressive syndrome with a significant anxiety component together with sleep disturbance, they offer a highly effective treatment strategy.

There is now good evidence to indicate that SSRIs are also effective in severe melancholic depression which requires inpatient treatment. The response to treatment with fluoxetine is similar to that seen in patients amitriptyline. Melancholic depression is associated with a broad spectrum of neuroendocrine disturbance. To begin with, many patients with melancholia are dexamethasone non-suppressors, indicating a significant disturbance of the hypothalamic-pituitary-adrenal axis. Furthermore such patients show disturbance in serotonergic mediated prolactin release. The latter can be demostrated by taking blood for baseline prolactin estimation and stimulating prolactin release with selective serotonergic drug d-fenfluramine. We have shown that with fluoxetine treatment in melancholia normalisation of dexamethasone responses takes place, together with normalisation of serotonergic mediate prolactin release, in the majority of patients.

There can be little doubt when one reviews the body of published literature that the SSRIs are effective across the broad range of the depressive spectrum, from the milder depressive episodes seen in a general practice setting to the severemelancholic episodes seen in inpatient psychiatric units.

SSRIs AUGMENTATION IN LITHIUM TREATED BIPOLAR PATIENTS

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Lithium augmentation to some antidepressants is considered effective in the treatment of resistant depressive syndromes. On the contrary, only a few reports deal with the effectiveness of SSRIs added to lithium therapy as a treatment for resistant major depressive episodes. The importance of the issue is due to the action of both lithium and SSRIs on the serotonergic neurotransmission. Our contribution is based on a research in a group of bipolar patients showing a depressive symptomatology during lithium therapy and tretaed with Fluoxetine.

Twenty-one fulfilled DSM-III-R criteria for bipolar disorders in the years 1991-1993. Twelve were females and nine males, with a mean age of 42.2 years (SD= 11.6). Their diagnosis was Bipolar I in eleven, Bipolar II in eight and Bipolar mixed in two patients. The mean duration of lithium treatment was 38.7 months (SD= 34.2) with a mean serum lithium level of 0.59 mmol/l (SD= 13.9). Their mean Hamilton Depression Rating Scale (HDRS) score before antidepressant treatment was 16.9 (SD= 5.3). Fluoxetine was added to lithium at a dose varying from 20 and 60 mg/day. The assessment was performed after a period of one month.

The efficacy of Fluoxetine augmentation to lithium in bipolar patients was assessed by the means of the HDRS total score variation. The mean HDRS total score after one month was 7.8 (SD= 5.7) with a highly statistically significant reduction from baseline ($p< 0.001$). The reduction of the HDRS total score was equal to or higher than 50% in 15 (65.2%) subjects. No statistically significant variation was found in the serum lithium levels before and during treatment with Fluoxetine.

Our results show that breakthrough depressions during lithium treatment can be successfully treated with Fluoxetine. The short period of time required for the improvement of the symptomatology may be possibly due to the synergistic effect of both therapies on the serotonergic system. Mild side effects included tension in one subject; insomnia in another one and vomiting in a third one.

Possible mechanisms involved are: increase of serotonergic transmission and the synergistic effect on the phosphoinositide metabolism.

SSRIs IN THE TREATMENT OF OCD AND OCD-RELATED DISORDERS: AN UPDATE

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Obsessive-Compulsive disorder (OCD) is characterized by recurrent and persistent, intrusive and distressing thoughts, images or impulses (obsessions) and/or repetitive behaviors that the person feels driven to perform (compulsions).

OCD is unique among psychiatric disorders in its specific response to pharmacological interventions. Benzodiazepines, dopamine blockers, non-serotonergic monoamine reuptake blockers and ECT all do not appear to be effective anti-obsessive treatments. To date only serotonin reuptake blockers were found in a double-blind, placebo controlled studies as an effective anti-obsessive medications.

Currently clorimipramine, fluoxetine, sertraline, fluvoxamine and paroxetine are used in OCD. As all of those medications are also antidepressants it is important to note that depression is not a prerequisite for their anti-obsessive effects as was demonstrated in studies with non-depressed OCD patients.

Despite the availability of effective treatment for OCD, several issues await investigation, such as the right dose, the length of maintenance therapy, the approach to treatment refractory patients, and the role of behavioral therapy and neurosurgical therapy alone and in combination with pharmacological treatment.

Preliminary reports suggest also a specific role for SSRIs in other disorders with obsessive and/or compulsive symptoms such as dysmorphophobia (body dysmorphic disorder), trichotillomania (hair pulling), hypocondriasis, restricter anorexic patients, subtypes of sexual compulsions and compulsive gambling.