Serotonin & Depression – Recent Advances in Understanding

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Depression is the fourth major illness in the western world and is predicted to rise to number two. More days are lost at work through depression and related illness than from any other cause. While drug treatment has improved over the years, mainly due to a reduction in side-effects rather than increased clinical efficacy, we still lack effective fast acting drug therapy. The great need is to understand the mechanisms involved in the long-term action of existing drugs so that we might more effectively target the key events. This talk will review our current understanding of depression with particular reference to the mechanism of action of antidepressant drugs.

The interest in serotonin and depression dates from the time when it was first shown that tricyclic antidepressant drugs prevented the reuptake of both serotonin and noradrenaline back into the pre-synaptic nerve endings. Studies on human suicide victims also indicated low serotonergic function. More recently the advent of the serotonin selective reuptake inhibitors (SSRIs) as successful antidepressant drugs has increased research activity into the role of serotonin in depression from two stand points: Is there evidence for serotonin dysfunction in depression and why do antidepressants take so long to be clinically effective when they work via activation of serotonergic systems in the brain?

Human studies using trytophan depletion clearly indicate when brain serotonin levels are reduced by preventing brain access to trytophan relapse can be induced in patients in remission from depressive symptoms. Neuroendocrine studies have shown $5HT_{1A}$ receptor activation increases prolactin and ACTH release and these neuroendocrine responses are blunted in depressives when activated by treatments that increase pre-synaptic serotonin release but not when using direct agonists indicating reduced pre-synaptic serotonin function in depression. Overall there is strong evidence for a

serotonergic dysfunction in depression involving decreased pre-synaptic depression at least there is also decreased noradrenergic and possibly dopaminergic function.

The SSRIs are rather similar in clinical efficacy to the older tricyclic drugs but with the advantage that they have fewer side-effects notably no muscarinic antagonism. They do however have other side-effects reflecting increased serotonergic function at $5HT_2$ (loss of libido) and $5HT_3$ (nausea) receptors. The real scientific interest in the SSRIs is whether by studying selective serotonin uptake inhibition we can understand the delay in clinical effect.

Blockade of serotonin reuptake results in increased synaptic serotonin and consequently activation of the inhibitory somatodendritic ($5HT_{1A}$) and terminal ($5HT_{B/D}$) autoreceptors resulting in reduced serotonergic function. It is suggested that increased serotonin function is only observed following desensitisation of these autoreceptors. The resultant increased serotonin release can then activate post-synaptic serotonin receptors, in particular $5HT_{1A}$, important in regulating responses to stress and aversive situations so increasing resilience and causing disinhibition to improve mood. It is now clear that this is not the complete story as SSRIs and other antidepressants also alter gene expression through activation of CREB and an effect of this is to increase release of BDNF as well as other neurotophic factors. These effects appear to occur in animals particularly within the hippocampus and dentate gyrus. This raises the concept that long-term antidepressant treatment may increase synaptic contacts and remodel 'brain wiring' in areas of the limbic system. It is interesting to note that analysis of the clinical data indicates that 2 years of treatment may be required for maximal benefit from antidepressant drugs.

There is increasing use of antidepressant drugs in children and if these drugs can alter gene expression and release of neurotophic factors there is an obvious need to very carefully evaluate their effect on the developing brain. This will be briefly discussed in the talk.