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Review Article

Depression: Review article

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ABSTRACT

To prove the post-natal depression model, the antidepressant sertraline, was assessed in rat mothers (n=14) divided into Prenatally Stressed (PS) and Non-Stressed (NS) groups. The data failed to support the hypothesis that 'the progeny of 10mg of sertraline-treated PS mothers displayed less anxiety than the progeny of vehicle-treated PS mothers'. The forced swim test (FST) was used to examine depressive-like behaviour in mice. Barley successfully increased mobility in mice exposed to the FST. Barley was antidepressant at low doses (0.8g/kg and upwards) if used subchronic; and at high doses (6.4g/kg and 12.8g/kg) if used acutely; (n=113, 56 acute, 57 subchronic-treated). Barley (6.4g/kg) was also able to alleviate the depressive-behaviour in mice induced by the Reserpine Test (n=114, 58 reserpinised, 56 non-reserpinised) and Social 'Defeat' Test (n=24, 8 vehicle undefeated, 8 barley defeated, 8 vehicle defeated mice).

To confirm that the anti-depressant effects of barley(6.4g/kg) were not simply due to increased locomotor activity in the FST, an Open Field Test(OFT) was undertaken (n=14,7 vehicle, 7 barley). Barley had no effect on locomotor activity and also caused no significant changes in weight (n=16; 8 vehicle, 8 barley). In mice, Barley (6.4 g/kg) significantly delayed the tremorogenic effects of Physostigmine (n=18, 6 control, 6 Physostigmine, 6 Physostigmine with barley); reduced bradykinesia induced by reserpine (n=18, 6 control, 6 vehicle, 6 barley treated); and was analgesic in nociception tests (n =20, 5 control, 5 barley, 5 pain, 5 pain with barley).

Overall, barley was seen to have many useful properties, though its effect in PND remains to be assessed.

Keywords: Depression, Anti-Depressants, Morbidity.

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INTRODUCTION

Depression is a complex and multifaceted disorder.[1] It is defined as a sustained emotional state that is characterized by sadness, low mood, misery, discouragement, hopelessness, emptiness, unhappiness, distress and pessimism.[2]

Depressive disorders are divided into three categories: Major Depressive Disorder, Dysthymic Disorder and Depressive Disorder Not Otherwise Specified. The symptoms of depression, apart from arising clinically, may cause significant distress to the patient's socializing activities or occupational skills. The symptoms are not the result of the physiological effect of substances such as illicit drugs or medications, or of general medical conditions such as hypothyroidism. Also, bereavement is not considered one of the causes of the symptoms.[2]

AETIOLOGY OF DEPRESSION

It has been suggested that the aetiology of depression is multifactorial as it is related to genetic factors, life events and medications. In terms of genetics, it is believed that some genetic factors are able to affect the functioning of the brain and make the person more vulnerable to depression.[3] In today's modern world, complicated life events may play a significant role in causing depression.[4] Also, several studies showed that stress at an early age could predispose an individual to develop depression in adult life.[5] Despite the long-standing clinical success of medications, they still have disadvantages as they can produce harmful side effects.[6]

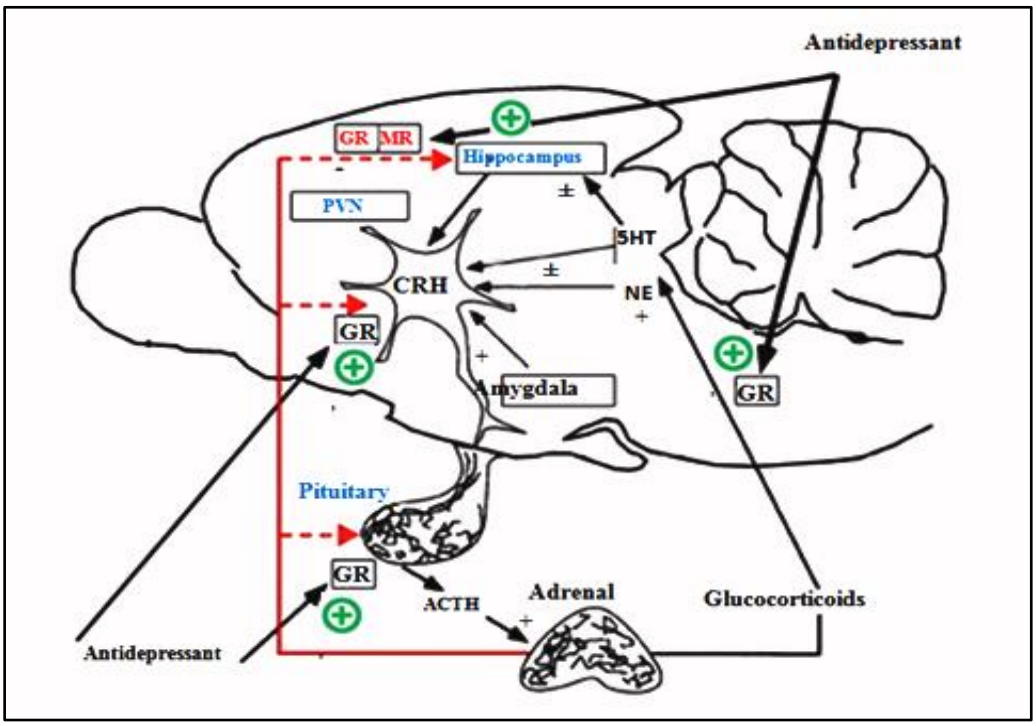
PATHOPHYSIOLOGY OF DEPRESSION

Famous candidates in pathophysiology have included the following:

Overexposure to cortisol, the monoamine hypothesis (these two hypotheses being those upon which we will focus, as they are relevant to the models chosen for experimental work presented herein), synaptic plasticity[7] and tryptophan depletion.[8]

MANAGEMENT OF DEPRESSION

The goal of treatment is to alleviate symptoms of depression, prevent relapses from occurring, improve quality of life and medical health status and decrease the economic burden of management.[9] Generally, depression treatment can be divided into pharmacotherapy and psychotherapy. Pharmacotherapy for depression includes the administering of antidepressant agents such as tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs) and selective noradrenaline reuptake inhibitors (SNRIs).[10] All these agents increase transmitter levels and can reduce depressive symptoms. However, there is disconnect between the timecourse by which the drugs increase neurotransmitter availability in the synapse (which is almost immediate), and the timecourse by which depressive symptoms are alleviated (which is usually in the region of 1-3 weeks after treatment onset). This suggest that there is a secondary mechanism that is important in antidepression pharmacotherapy.[11] In mild depression, antidepressant drugs should not routinely be used in the treatment. There are some exceptions to this rule, such as patients who have a history of moderate or severe depression. Conversely, with moderate and severe depression, antidepressant drugs should be routinely offered to all patients.[12] Psychotherapy is an interpersonal intervention used by psychotherapists. Some forms of psychotherapy seek to identify underlying problems (psychodynamic therapy), while other forms look at patterns of thinking and beliefs that affect mood (such as cognitive-behavioural therapy). Psychotherapy tries to offer solutions to cope with these issues. Combinations of psychotherapy and pharmacotherapy have been proved to have significant value.[13]



⊕, + = Stimulate; — = Inhibite; 5HT = Serotonin; ACTH = Adrenocorticotropic hormone; CRH =Corticotrophin-Releasing-Hormone; GR = Glucocorticoid receptors; MR = Mineralocorticoid receptors; NA = Noradrenaline; PVN =Paraventricular nucleus of the hypothalamus.

Figure 1: Antidepressants acting on the HPA axis (Adapted from Barden et al., 1995)[37]

PHARMACOTHERAPY OF DEPRESSION

One possible mechanism for the antidepressant effects of pharmacotherapy is normalization of HPA axis activity through decreased CRH mRNA levels in the PVN of the hypothalamus.[14] There is a link between these changes and increased levels of mRNA for the hippocampal GR[15] and MR.[16] Figure 1 shows their sites of action.

In fact SSRIs are the most widely prescribed antidepressants in the world for severe cases.[17,18] They have enormous value in the treatment of depression[19] and have numerous advantages over older medications like the TCAs, such as fewer side effects, and safety in overdose.[20] During pregnancy the use of SSRIs and TCAs suggests that they are relatively safe for both the mother and fetus.[21] Common side effects of the SSRIsare orgasmic failure, nausea and insomnia.[22] They exert their effect by inhibiting 5HT reuptake, but act with greater specificity than TCAs in this regard.[23] Notably, sertraline is a good example of an SSRI.

OVERVIEW

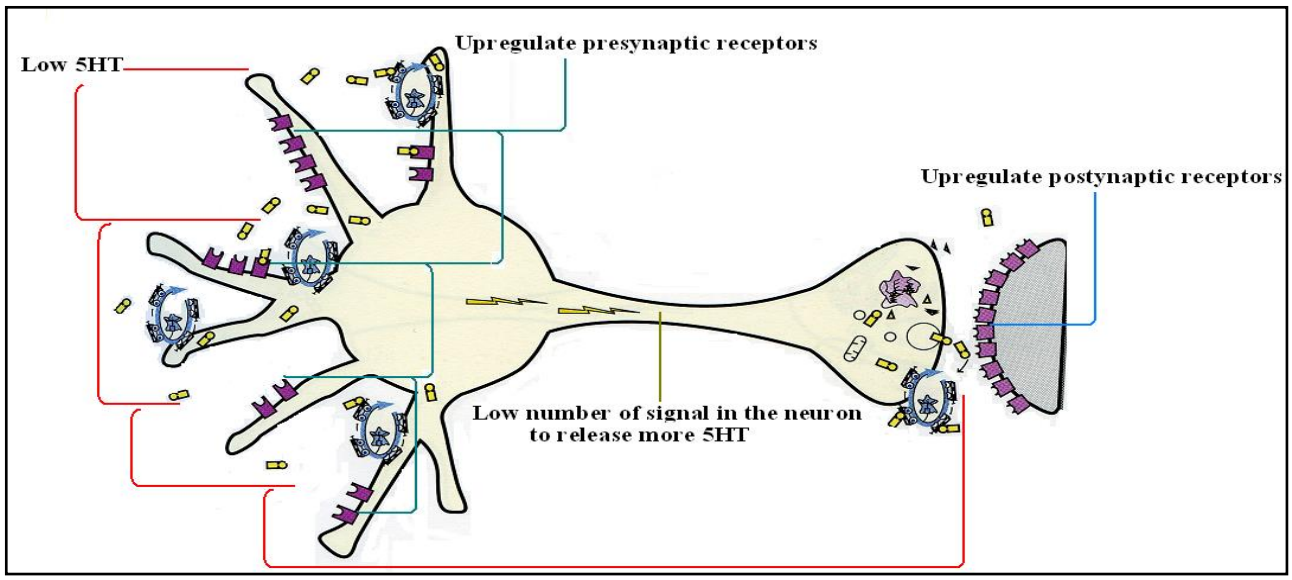
Sertraline hydrochloride is an SSRI antidepressant drug; it has the brand name Zoloft® (Glassman et al., 2002).[24] It produces marked improvements in quality of life measures.[25] For example, in terms of efficacy, it and fluoxetine have comparable antidepressant efficacy in the treatment of major depression. However, its advantages far outweigh those offluoxetine in severe depression sufferers.[26, 27] In terms of tolerability, it is considered to be much better tolerated than fluoxetine.[28]

MECHANISM OF ACTION

In the depressed state, the monoamine hypothesis of depression states that 5HT may be deficient, both at the presynaptic somatodentritic area near the cell body and in the synapse itself near the axon terminal.[29] Also, as a compensatory mechanism, the number of receptors will be increased on the surface of neurons (upregulation) at presynaptic receptors[30], and at

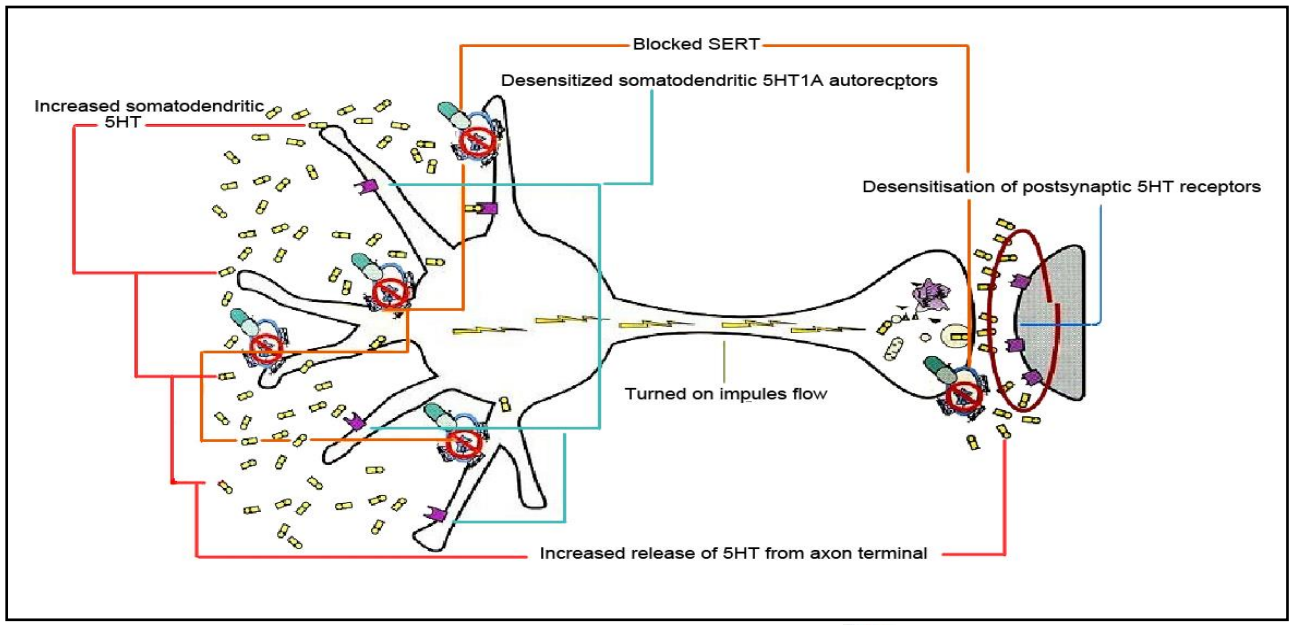
postsynaptic receptors.[31] Additionally, neural firing rates for this neuron may also be dysregylated, leading to a decrease in 5HT release.[32] (Figure 2)

When sertraline is given acutely, it has a great affinity with the serotonin transporter (SERT), so the latter transporter is blocked of 5HT both at the axon terminals and somato-dendritic areas of serotonergic neurons. SERT is an integral membrane protein that arranges transport of 5HT from synaptic spaces into presynaptic neurons (reuptake).[33] Once taken up into the presynaptic terminal, 5HT may be degraded by MAO to 5-HIAA, its major metabolite (termination of 5HT action), or it can be repackaged into secretory vesicles by the vesicular monoamine transporter for subsequent reuse .i.e. the SERT is responsible for the clearance and recycling of 5HT in the brain.[34] Over time, the increased 5HT levels acting at the somatodendritic 5HT1A inhibitory autoreceptor (which acts to reduce 5HT neuronal firing and 5HT release) cause them to decline in that autoreceptor number (receptor downregulation) and become desensitized.[35] This desensitization occurs because the increase in 5HT is recognized by the presynaptic 5HT1A inhibitory autoreceptors, and this information is sent to the cell nucleus that causes these same receptors with specific regulation to become desensitized over time. The onset of therapeutic actions of sertraline correlates with the time course of this desensitization. Once the 5HT1A somatodendritic inhibitory autoreceptors are desensitized, 5HT can no longer effectively turn off its own release. Consequently, the 5HT neuron is disinhibited. This results in an increase in neural impulse flow and also the release of 5HT from the axon terminal, leading to a 5HT build-up in synapses.[36] The final step causes the postsynaptic receptor to be desensitized as well (Figure 3).



;5HT = Serotonin; = Serotonin 1A(5HT1A) autoreceptor ; = Serotonin postsynaptic receptor; = Serotonin transporter (SERT)

Figure 2: Depressed state theoretical effects on 5HT neuron (Stahl, 2008)[38]



;5HT = Serotonin; =Serotonin 1A(5HT1A) autoreceptor; = Serotonin postsynaptic receptor; = Serotonin transporter (SERT); =Sertraline

Figure 3: Mechanism of action of sertraline (Stahl, 2008)[39]

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