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Original Article

Current Concepts About Mechanisms Of Action Of Antidepressant Drugs.

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ABSTRACT

In the context of Psychiatry, Depression is characterized by sadness and lowness of mood (hence, it is a disorder of mood), feelings of worthlessness and hopelessness; and it may also include body-pain, disturbance in sleeping and eating patterns.[1]

Keywords:
Mechanisms , Antidepressant Drugs , Psychiatry.

Introduction

There are various drugs available in the market for the treatment of depression. These drugs basically act by increasing the actions of certain monoamine transporters viz Noradrenaline (also known as norepinephrine, NA), Dopamine (DA) and Serotonin (5HT) in the brain. In depression, certain areas of limbic system and cortex in the brain suffer from deficient actions (decreased post-synaptic action on nervous tissue) of these monoamines. Antidepressant drugs combat the problem of depression by increasing the actions of these monoamines in the concerned areas. 2,3

Exact mechanisms of their actions are still under research. In this review article we have tried to explain the most widely accepted mechanisms of their actions in a simple and lucid way.

Possible mechanisms of action of antidepressants:

These drugs mainly increase the post-synaptic activity of monoamines by inhibiting their pre-synaptic reuptake in the nervous tissues. Important modalities in this context are-

A.Inhibition of the reuptake of neurotransmitters-

1)Noradrenaline reuptake inhibition 4,5- when the antidepressant is started, first of all, it causes upregulation of presynaptic α2 autoreceptors in the noradrenergic neurons. These receptors are for negative feedback, i.e. these receptors inhibit the release of NA from the presynaptic terminal. Now, because of upregulation of these a2 receptors, NA starts getting accumulated in the presynaptic terminal. After 2-3 weeks, antidepressant drug opens the NET (norepinephrine transporter) on the presynapse and downregulates the presynaptic a2 receptors.

2)Now, the result is, NET starts sending the NA in the synaptic cleft from the presynaptic terminal (while the usual task of NET is the reuptake of NA, i.e. NET takes-up NA from synaptic cleft and sends it in the presynaptic terminal), because NET works according to the concentrations of the NA on either sides. Since the concentration of the NA is more in the presynaptic terminal, so, it will be sent to synaptic cleft by NET. Now, NA works on postsynapse to provide antidepressant response. Side by side, postsynaptic a1 receptors are

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upregulated by antidepressants, NA works on these receptors to provide antidepressant response. That's why, clinically appreciable response is achieved in 2-3 weeks with these antidepressents.

However, a big amount of NA is now accumulated in synaptic cleft because of aforementioned reason; so, according to the law of concentration gradient, NA will be taken back by NET and will be sent in the presynapse. If this event takes place, antidepressant response of NA will start decreasing. But, by this time, antidepressants also stimulate 'locus ceruleus (in the pons)' which is a source of NA. Thus, there starts secretion of huge amount of NA from locus ceruleus. This NA reaches the presynapse and now again, in comparison to synaptic cleft, there will be more NA in the presynapse and NET will start sending this NA (came from locus ceruleus) into synaptic cleft. Again, NA will start working on postsynapse and will exert its antidepressant response.

Also, there are certain ß receptors which have inhibitory action on some 5HT-postsynaptic and presynaptic heteroreceptors. These 5HT receptors repress the feeling of depression. When these 5HT receptors are disinhibited (because now the inhibitory effect of ß receptors has been suppressed by antidepressant), they also exert their antidepressant response.

3)Serotonin reuptake inhibition 6 - If antidepressant drug is working on 5HT-neurons, basic sequences are same as those in case of NA reuptake inhibition. Here, in case of 5HT neurons- in place of presynaptic a2 receptors, there will be 5HT1A receptors 8; in place NET, there will SERT7 (serotonin transporter); in place of 'locus ceruleus', there will 'raphe nucleus (found in brain stem, rich source of 5HT)'; and, in place of postsynaptic ß receptors (which were inhibiting 5HT receptors with antidepressant action), there will be 5HT2A receptors.

Drugs may preferentially inhibit the reuptake of NA or 5HT; or, combined inhibition is also performed by some drugs. Mirtazapine 9 is an antidepressant, which inhibits a2 autoreceptors (i.e. located on presynapse of noradrenergic neurons and inhibit the release of NA from presynaptic terminal) and heteroreceptors (i.e. located on presynapse of serotonergic neurons and inhibit the release of 5HT from presynaptic terminal). Thus, release of NA and 5HT is increased from the corresponding presynaptic terminals to exert antidepressant action.

B.Effects of glutaminergic and dopaminergic transmissions-

'Tianeptine' is a drug which enhances the release of DA in the mesolimbic pathway. But till date it is not clear on which DA-receptors it acts. It also inhibits the glutaminergic transmission (overactivity of glutamate may cause 'stress associated neuronal remodeling') by acting on NMDA and AMPA receptors and reduces the risk of 'stress associated neuronal remodeling'.10, 11, 12

C.Snare complex theory13-

Literal meaning of 'snare' is 'a trap for catching birds or animals, typically one having a noose of wire or cord'. According to this theory, antidepressants cause opening of calcium-channels on the presynapse which cause influx of calcium-ions inside the presynaptic terminal which results in depolarization. Due to depolarization, vesicles filled with the neurotransmitters coalesce with one another (also known as 'docking of vesicles') and become a big single vesicle. This big vesicle comes to the neuronal membrane and gets fused with the membrane. Thus, the big vesicle becomes an entity of neuronal membrane and neurotransmitter inside it is released in synaptic cleft (exocytosis). Here, the docking of vesicles is facilitated by a protein known as 'snare'. But this theory is still in the phase of infancy and researches have been going on in this aspect.

Conclusion:

Despite all these researches to support monoamine-hypothesis, these conjectural mechanisms are unable to explain why a significant proportion of patients (>40%) don't give adequate response to the therapy. Also, apart from the monoamine-theory, there is one more important hypothesis about the genesis of depression, i.e. BDNF (Brain-derived

neurotrophic factor)-theory. According to this theory, due to deficiency of BDNF; growth, development and differentiation of neurons and synapses are hampered. But, till date, we have only a very few drugs which possibly (not certainly) act on this modality, e.g. Tianeptine probably increase the level of BDNF. Thus, however, monoamine hypothesis is most widely accepted, more researches are needed in this direction to elucidate the exact mechanisms of action of antidepressant drug. Last but not the least, more work is needed to unveil the various etiologies for the genesis of depression so that more effective drugs may be designed.

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