Depression and bipolar disorder.

Depression is the most common of the affective disorders which can be divided into two types. The unipolar depression, in which the mood changes are always in the same direction. And bipolar disorder, in which depression alternates with mania. Mania is in most respects exactly the opposite, with excessive exuberance, and enthusiasm.

The common symptoms of depression

The symptoms of depression include emotional and biological components. Emotional symptoms include low mood and excessive rumination of negative thoughts. Biological symptoms include retardation of thought and action, loss of libido, sleep disturbance and loss of appetite.

Pathology of depression

Depression is a polygenic disorder where several individual genetic variations, as well as environmental factors, contribute to the disorder. Depression is attributed to the dysfunction of circuitry linking different parts of brain regions. Which most contain the prefrontal cortex, amygdala and hippocampus disorders. The theories to explain depression are the monoamine hypothesis, neurotrophic hypothesis and excitatory synapses hypothesis.

The pathology of depression is intrinsically linked to the dysregulation of the Hypothalamic-Pituitary-Adrenal (HPA) axis, regions that control CRH and ACTH feedback control which is central to the body's response to stress. Chronic activation of the HPA axis leads to sustained high levels of cortisol, a stress hormone that can alter brain function and mood, laying the groundwork for depression. This alteration can diminish neurotransmitter levels, which is the core of the monoamine hypothesis. This well-established theory suggests that a deficit in monoamines—namely serotonin, norepinephrine, and dopamine—contributes to depressive symptoms. Serotonin is released from neurons originating in the dorsal raphe nucleus, which projects to many brain regions involved in depression: hippocampus, amygdala anterior cingulate cortex, and nucleus accumbens. SSRIs, which increase serotonin in the synaptic cleft, support this hypothesis through their therapeutic effects.

Simultaneously, the neurotrophin hypothesis posits that depression is characterized by reduced neuroplasticity, implicating brain-derived neurotrophic factor (BDNF) in the disorder. BDNF is essential for neuron survival, development, and synaptic plasticity. A high level of cortical release will promote neural apoptosis in the hippocampus prefrontal cortex. Conversely, the secretion of monoamine transmitter and expression of BDNF could induce neurogenesis. So stress-induced high cortisol levels negate the effection of BDNF, then leading to the atrophy of hippocampal neurons and impaired functioning of neuronal circuits associated with mood regulation. Patients with depression often have a high level of cortisol and have increased volume and activity in the amygdala but decreased volume and activity in the hippocampus.

The excitatory synapse hypothesis extends these concepts by focusing on the dysfunction in glutamatergic neurotransmission and synaptic strength. It is bolstered by the rapid antidepressant effects of agents like ketamine, which, as an NMDA receptor antagonist, can quickly strengthen synaptic connections. This is thought to occur through the upregulation of AMPA receptors, contrasting with the slow-acting nature of conventional antidepressants. Also, electroconvulsive therapy(ECT), electromagnetic therapy, deep brain stimulation and vagus stimulation, are effective usually as a rapid antidepressant effect as well.

Current treatment

Antidepressant drugs fall into the following categories. The first generation of classic tricyclic antidepressants(TCAs) such as clomipramine. They can inhibit the NA and 5-HT reuptake. These drugs are still very widely used although they have some unwanted side effects: sedation, and anticholinergic effects. The second generation of monoamine uptake inhibitor is SSRI (serotonin selective reuptake inhibitor) they are all highly selective for 5-HT, such as citalopram and fluoxetine. The side effects of these SSRIs are nausea, diarrhoea, agitation, insomnia and so on. Besides, NA-selective inhibitor bupropion is also used to treat depression associated with anxiety.

The rapid onset antidepressant action is NMDA antagonist. The effect of Ketamine, an NMDA antagonist can block the NMDA receptors after taking in 2 hours and the effect can last for 2 weeks. There are three hypotheses to explain the long period lasts. First, ketamine will preferential action on interneurons results in NMDA receptors blocking only inhibitory neurons, so it increases excitation due to reduced inhibition. Second, ketamine can block the relief of ongoing spontaneous NMDAR activation which suppresses the plasticity mechanisms. So ketamine inhibits the pathway to increase excitation. the last, non-NMDAR dependent activation and potentiation of AMPARs through ketamine metabolites which activate the synapse plasticity.