



Biochemical Causes of Depression

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Monoamine Theory of Depression

- At about the same time as when antidepressants were discovered in the 1950s it was noted that reserpine when administered to some patients caused symptoms of depression. Subsequent studies revealed that reserpine depleted neuronal monoamine neurotransmitters, noradrenaline (NA), dopamine (DA) and serotonin (5-HT), and that this was probably the reason for its 'depressant action'.
- Conversely, tricyclic antidepressants and monoamine oxidase inhibitors were found to enhance monoamine neurotransmission by increasing the availability of neurotransmitters in synapses (the connections between neurons). Imipramine was found to do this by inhibiting the neuronal reuptake of noradrenaline and serotonin, while the monoamine oxidase inhibitors achieved the same by inhibiting their degradation. It was these observations that led to the monoamine theory of depression.
- The theory suggested that depression was a consequence of diminished neurotransmission involving monoamines (NA, DA, 5-HT) due to a decrease in their concentrations or because of reduced sensitivity to their actions on receptors.
- However, the biochemical changes found in depression have not been explained by a single model or theory, and it is now thought probable that many neurotransmitter systems, acting at various sites within the brain, contribute to the pathogenesis of depressive illness.

'Multi' not 'Mono'

It is because of this that we believe the principal neurotransmitters 5-HT, NA and DA all contribute to the development of depressive symptoms and that they do this in a fashion in keeping with our structural sub-typing model of depression.



- Therefore, psychomotor changes observed in psychotic depression and melancholia are thought to be principally the consequence of dopamine dysfunction, while many of the remaining melancholic features reflecting disturbances of drive, energy and volition are related to noradrenergic dysfunction.
- The non-melancholic features of depression (including mood, sleep and appetite disturbances), which invariably overlap with other syndromes such as anxiety states, obsessive-compulsive disorder and eating disorders, are associated more so with serotonergic dysfunction.

Regulation Not Amount

Clearly, it is simplistic to assign the cause of a complex and varied illness such as depression to the dysfunction of only one, two or even three neurotransmitters.

- However, measurements of neurochemicals in the blood and brain tissues and fluids, findings from endocrine and receptor studies, and other pharmacological research all strongly implicate serotonin, noradrenaline and dopamine in the pathophysiology of depressive disorders.
- Therefore, we suggest that the depressive disorders may be better understood as reflecting neurotransmitter regulation system dysfunction as opposed to a simple increase or decrease in activity of a particular neurotransmitter and that neurotransmitter systems themselves should perhaps be regarded as 'regulators' of mood – emphasizing the dynamic processes at play.

Brain Imaging

Imaging techniques capable of demonstrating changes in brain function – in particular positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) – have been used in recent years to identify brain regions that might be involved in depression. Because of the possibilities offered by these techniques our Institute is making a major research investment in such imaging studies.

Brain Regions Involved in Normal Emotional Experience

Understanding the normal can often help us to understand the abnormal so imaging techniques have been used to examine brain regions involved in normal mood.

- Prior to the introduction of these technologies, theories about brain areas involved in mood derived largely from the traditional 'lesion model' of neurology. In other words, disturbances in mood were related to particular regions damaged by conditions such as strokes or brain injury.



- Using imaging technologies, researchers have employed films or pictures to produce positive or negative emotions. In a recent study, a number of evoked emotions were seen to produce activation of a region at the front of the brain. The fact that a number of different emotions caused activation of this area suggested that this region mediated the processing of emotion-related meanings.
- In another study the same medial prefrontal cortex region was activated by happiness, sadness and disgust. Other areas in the brain were activated also: the thalamus, temporal structures and the anterior insular.

Such investigations of the brain processes for 'normal' emotions will ultimately help understanding of the regions involved in abnormal mood states, such as depression.

Brain Regions Involved in Depression

- Brain imaging techniques such as CT or MRI scans have been used to look at any changes in brain structure in depression. They have found differences in regions thought to be involved in the control of mood.
- Mapping any such changes can be of particular use in the diagnosis and treatment of any depressive disorder that occurs later in life.
- Functional studies using PET and SPECT have both demonstrated reduced blood flow in areas of the brain during an episode of depression, particularly in patients who have a strong family history of unipolar or bipolar illness.
- Depression occurring in later life may be more of a 'vascular depression', arising from risk factors that come into play with older age.