Psychiatric Medicine 3
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Neurobiology of Depression

Mood Disorders (depression and bipolar disorder) start at an early age and are difficult to diagnose in youth. They can be confused with normal teenage behavior, drug use or other psychiatric illnesses. They are characterized by recurrent episodes or chronic illness. With increasing age, the interval between episodes gets shorter and the episodes tend to last longer. Therefore, the period of wellness gets shorter as the person gets older.

If the illness isn't treated expeditiously, the individual pays a price initially in school because they find it very difficult to study, concentrate and learn when suffering from depression.

Friendships are affected and tend to deteriorate. Depressed individuals don't want to interact with friends and family and they think that family and friends don't want to be with them.

People in a **job** who are depressed find it difficult to work. They have to drag themselves out of bed, so they have a great deal of difficulty getting to work on time. Just getting out bed and having to take a shower sometimes feels like an enormous effort. This also applies to an individual who may be traditionally quite energetic and cheerful. When the economy takes a downturn people with mood disorders tend to get fired early and often.

Marriages suffer. It is difficult to be married to somebody who finds it hard to get up in the morning and go to work, who has lost all interest in sexual relations, whose concentration is poor, whose self-esteem has fallen through the floor, who doesn't want to socialize, etc.

Finances and even **physical health** can suffer. For example, individuals who have or develop an untreated mood disorder and at the same time have a myocardial infarction (MI) have a 4 – 6 fold greater mortality from a fatal sequelae to the MI.

Bipolar disorder is characterized by periods of **depression** preceded by **manic episodes**. Sometimes the manic episodes are actually hypo manic episodes. This is important to keep in mind when a patient presents to the doctor in a depressed state. The doctor should always ask if the patient has had a high as well. Sometimes the episodes can become very frequent with four or more episodes in a year. Other times the episodes can be co-mingled so the person switches from a high to a low within days or hours. This might occur during the clinical interview, i.e. the patient may seem high and low at different times during the same interview. In these situations the illness becomes harder to treat.

Depression or mood disorders are **a brain illness**. There are significant **genetic** as well as developmental causal factors. These are manifest at several stages throughout life.

There are **genetic as well as non-genetic effects** that operate **in utero**. These tend to produce developmental changes in the brain that persist throughout adult life. These changes are not

necessarily manifested immediately as psychopathology. Illness might not begin to emerge until adolescence or later in the 20s, 30s, or 40s.

Generally, **the more relatives an individual has with mood disorders, the earlier the onset of a mood disorder in that person**. In other words, the higher the familial or genetic loading for mood disorders, the earlier the illness begins in life.

The serotonergic system plays a role in brain development, and, in adulthood, it plays a role as a regular neurotransmitter system that modulates behavior.

The Neurotransmitter Deficiency Hypothesis Of Depression:
There are **six neurotransmitters** that are hypothesized to be **deficient** in depression. Not all of them are necessarily deficient at once, but one or more may be deficient in any particular individual. **The granddaddy of them all is serotonin**. Also implicated are norepinephrine, dopamine, GABA, BDNF, and somatostatin. There are **some neurotransmitters** that are **in excess**, or thought to be in excess such as acetylcholine, substance P, and corticotrophin releasing hormone (CRH) which is a neurotransmitter in the brain.

Serotonin: Every time that serotonin is released a little bit is broken down into 5-hydroxyindoleacetic acid (**5-HIAA**). The serotonin that is not broken down is recycled for future use. The more serotonin released, the more that is broken down. Studies suggest that **there are lower concentrations of 5-HIAA in the CSF of people who are depressed**. Lower concentrations of 5-HIAA suggest lower serotonin levels.

The level of 5-HIAA is **under genetic regulation**. It is a candidate for the genetic cause of depression. However, it is **also affected by parenting**. Monkeys that are raised by their peers instead of their mothers (like boarding school or nursery school) have lower CSF 5-HIAA levels compared to monkeys raised by their mother. These decreased CSF levels persists into adulthood even if after a while you take them out and put them back in with their mother. Therefore, **an adverse rearing experience involving deprivation in childhood, at a critical phase in development, can reset the serotonin system to lower concentrations that will persist into adulthood and be a potential cause of psychopathology**.

Genes can interact with **the environment**. A monkey or a person with genetically robust serotonin activity that undergoes a period of childhood deprivation in terms of parenting has a subsequent drop in their serotonin level. However, given their initially high levels, the drop may not decrease their serotonin levels to abnormally low values, and the person may not show any deviation from normality in terms of behavior as an adult. If, on the other hand, the individual had genetically low serotonergic function they might then be vulnerable to a psychiatric illness after going through an adverse childhood experience. Therefore, genes can protect an individual from the effects of the environment or they can make them susceptible to the effects of the environment.

Many drugs cause the release of serotonin or a rise in serotonin levels intersynaptically. One of the consequences of serotonin release or of increased serotonin levels is that **prolactin** is released into the blood. Prolactin levels in the blood can be measured very readily. This response

is blunted in people who are depressed as well as in people who have been well for years after an episode of depression. **Individuals that had an episode of major depression in the past and were well for many years had similar abnormalities in their serotonin system as those individuals that were in the midst of a clinical depression.**

An artificial **serotonin deficiency** can be induced in normals by giving a drink that causes the **depletion of the amino acid tryptophan** in the brain. The drink contains large neutral amino acids that look like tryptophan and compete for the same transporter across the blood brain barrier into the brain. The brain needs a constant supply of tryptophan. If the system is saturated with other competitors a sudden drop in tryptophan results. Within 4-6 hours the brain serotonin levels may drop by as much as 50%.

When these drinks are given to people that are depressed or in the middle of a depression nothing happens. However, if the drink is given to them after they respond to antidepressant treatment, or if you give it to them years after they responded to antidepressant treatment and are not taking any antidepressants, a significant proportion of them will develop a recurrence of depression. This happens only transiently, for a few hours. Therefore, a problem has to be present because it happens particularly in people with a history of depression and in people who have first-degree relatives with a mood disorder but have not reported depression in themselves.

This provides more evidence that there is a serotonin abnormality between episodes as well as during episodes, and it may explain why the episodes are recurrent. It also may explain why **treatment is necessary in an ongoing fashion** in order to prevent relapse back into an episode. This is why **patients are treated for at least 6 months**, and it also may explain why people have future episodes unless they take the medication continuously.

Hyperactive Stress Systems:
There is an important interaction between the serotonin system and one of the brain's major stress systems the **hypothalamic pituitary adrenal axis** (HPA). The hypothalamus releases **corticotrophin releasing hormone** (**CRH**) which stimulates the pituitary to release **ACTH** which stimulates the adrenal glands to release **cortisol** (the most common human corticosteroid).

CRH and cortisol are found to be elevated in severely depressed patients and is probably proportional to the severity of the illness. The feedback inhibition that is supposed to regulate the system, or one component of it, is defective and doesn't suppress the release of CRH, ACTH or cortisol properly. **Dexamethasone**, an artificial corticosteroid, is given to patients to check the feedback inhibition of the HPA axis. During a depressive illness the system is stuck in overdrive.

Corticosteroids have actions in brain regions like the hippocampus. In the hippocampus there is a very important serotonin postsynaptic receptor, the **5-HT1A receptor**. Corticosteroids reduce the numbers of these receptors, and when elevated chronically probably damages the hippocampus making it both smaller and less responsive to activation by the serotonin system. This is because **corticosteroids shut down or reduce the number of 5-HT1A receptors**. It is suspected that the same thing happens to a lesser extent in the prefrontal cortex.

Many people have studied **platelets** over the years. Platelets are used for forming platelet plugs. They plug holes in blood vessels. **Serotonin mediates the shape change function of the platelet**. Therefore, it may be one of the factors explaining why there is an increased risk of death from MI in people with major depression.

In the last few years brain imaging has allowed direct visualization of the serotonin system. There are two ways of doing this. One way is to visualize the serotonin transporter that is located in the presynaptic serotonin nerve terminal. That is where all **selective serotonin reuptake inhibitors** (**SSRI**s) bind (e.g. Prozac, Zoloft, Paxil, etc.) which all work by blocking or competing for the transporter and slowing the reuptake or the recycling of serotonin after it is released. Much of the transporter is found in the anterior cingulate gyrus. Another way to look visualize the brain serotonin system is by looking at the 5-HT1A receptor that is regulated by the excessive amounts of corticosteroids in depressed people.

In postmortem brains of depressed individuals there is a 20 – 30% **deficiency of the serotonin transporter** all over the prefrontal cortex. This means that there is a very widespread deficiency of serotonin activity in people with a history of depression. This can be shown in living subjects using **PET scans** with positron emitting isotopes attached to specific SSRIs. There is less prefrontal cortex binding in depressed patients compared to controls. PET scans can therefore be used to objectively diagnose these kinds of illnesses.

The **5-HT1A receptor** is found in many brain regions as a major receptor that serotonin activates or binds to. It is also found on serotonin cell bodies in the midbrain where it functions as an **auto receptor**. When serotonin is released some binds the auto receptor and shuts off the firing of serotonin. It provides a **feedback mechanism to prevent continuous firing**. On PET scans receptor binding can be quantified. **In depressed patients there is a deficiency of this 5-HT1A receptor binding** with a particularly striking deficiency in the hippocampus and in some other brain regions as well. The defect is **greater in women than in men**. Maybe this is explained by the corticosteroid defect. Maybe there are other factors that have not been identified. Maybe it is due to estrogen because estrogen modulates the amount of 5-HT1A binding. Either way it is seen that there is a deficiency presynaptically in the amount of serotonin released and postsynaptically in certain key serotonin receptors.

Summary so far: There is a serotonin abnormality. Not enough serotonin is released. This is why CSF levels of 5-HIAA are low. This is why transporter binding is low. And there are postsynaptic abnormalities involving the 5-HT1A receptors. The abnormality is as striking during episodes as it is between episodes. This may explain the potential for recurrent episodes of illness. It probably starts even before the person has the first episode and may be determined by both genetic and childhood parenting experiences. What is important about the serotonin system is that it is a neurotransmitter and also plays a role in brain growth and development. Evidence suggests that abnormalities of the serotonin system can affect the number and the size of neurons that the serotonergic system innervates. It plays two roles. In development is has an important role in ensuring adequate brain growth and maybe even as an adult it may play a role in maintaining the size of the brain. Two important systems that the serotonergic system innervates are the cell bodies of noradrenergic system neurons in the brain stem and the GABAergic system in the brain.

There are two main neurotransmitters in the cortex. One is glutamate and the other is GABA. **The serotonergic system mainly directs its attention to the GABAergic system rather than the glutamatergic system.**

In some studies **the noradrenergic system** has appeared to be overactive in depression while in other studies is has appeared to be under active. Postmortem studies have shown that people with histories of depression have fewer noradrenergic neurons. The system's capacity to respond to demand is reduced. More recently it has been shown that people who have had adverse childhood experiences tend to over respond to stress (e.g. they release too much norepinephrine or too much cortisol, etc.). A stressor that may not elicit any response in a normal individual may therefore elicit an excessive response in individuals that have had adverse childhood experiences or who may be predisposed to depression.

If a person with low norepinephrine levels over-responds to stress, they will release excessive amounts of norepinephrine and will quickly deplete their norepinephrine stores. Continuous stressors might induce feelings of helplessness and hopelessness in individuals who are depressed due to their depleted norepinephrine levels. Therefore, **there may be phases in depressive illness depending on when the person is assessed**. At one point they may manifest the excess release of norepinephrine and at another point they may be manifesting the consequences of the excess release, which is depletion. **Depletion of norepinephrine induces a depressed state in individuals who have a history of depression, but not in healthy controls.**

Much less is known about **dopamine**. It may be a cause of depression in some individuals because people with Parkinson's disease sometimes will develop a disproportionate depression. There are some agents that raise dopamine levels that have proven to be useful antidepressants. There is also some preliminary evidence that homovanillic acid (HVA) which is the breakdown product of dopamine is deficient in some depressed patients. Therefore, **there is some evidence suggesting dopamine deficiency in some patients may potentially cause depression and dopamine elevation in some patients may be a useful antidepressant**.

GABA may be a very important neurotransmitter in mood disorders. A few studies have shown that CSF levels of GABA are lower in depressed patients. There is postmortem evidence that **there are fewer GABA neurons in individuals with histories of mood disorders**. There is more recent evidence from brain imaging that there is less GABA in the cortex of depressed patients.

Remember that the serotonin system has most of its terminals on the GABAergic neurons. There are many GABAergic neurons in the **anterior cingulate gyrus** where many serotonin neurons project. Another area that has a strong serotonin input is the **entorhinal cortex**. There are GABA neuron deficiencies in these two areas in individuals with bipolar disorder. There is also a loss of neuronal density in the prefrontal cortex in individuals who have a history of a major depression. Evidence suggests that this loss in density is due primarily to GABAergic cell loss and not pyramidal cell loss. Recently it has been shown with magnetic resonance spectroscopy that there is less GABA in the occipital cortex in people with mood disorders.

It is not known if there is a connection between the finding of fewer GABA neurons and less serotonin input. It is hypothesized that the number of GABAergic neurons may have required a certain level of serotonin input during development. If the serotonin system is genetically compromised it might not provide the necessary input during brain development, and this might lead to fewer GABAergic neurons or to a reduction in the GABAergic system's functional capacity. In order to investigate the hypothesis children would have to be analyzed to see if these abnormalities are present before they develop a mood disorder.

It is not entirely clear why it is that some people have **manic episodes**. It is believed that **the serotonin deficit is a predisposing abnormality to both highs and lows**. It is believed that the GABA deficit is predisposing to both depression and manic episodes. **Anticonvulsants** are used as **mood stabilizers** and as **anti manic agents** (e.g. depakote). Maybe increased norepinephrine and dopamine activity switch the direction of function and therefore precipitates mania.

Tyrosine hydroxylase is the enzyme that **makes norepinephrine and dopamine**. It is the regulating enzyme for both neurotransmitters. The **locus ceruleus** is where the cell bodies of noradrenergic neurons reside. In postmortem brains of unmedicated **depressed bipolar patients** there is **less tyrosine hydroxylase** in the locus ceruleus when compared to controls. In the **manic state** there is **more tyrosine hydroxylase** when compared to controls. When bipolar patients are treated with the mood stabilizer lithium their brains appear indistinguishable from normal controls. Therefore it is believed that **the noradrenergic system is much more state dependent in its functionality and it is a candidate neurotransmitter system for explaining the manic phase of the illness**.

Antidepressants:
Classically antidepressants **increase serotonergic function** by raising the amount of serotonin in the intersynaptic cleft. That can be accomplished by an SSRI-like action blocking the serotonin transporter and slowing down the reuptake of serotonin. Therefore the same amount of serotonin hangs around longer in the intersynaptic cleft and, as a result, the serotonin signal is magnified.

Monoamine oxidase inhibitors (MAOI) block monoamine oxidase (MAO) the main enzyme in the catabolism of serotonin.
Lithium somehow enhances serotonergic activity.
Tricyclic antidepressants basically block transporters.

Another antidepressant approach is to **enhance norepinephrine or dopamine** function. This can be accomplished by giving a **norepinephrine reuptake inhibitor** (NERI) or an MAOI because MAO also breaks down norepinephrine and dopamine.

Electro convulsive therapy (ECT) probably acts by increasing the number of receptors rather than the amount of transmitter and by enhancing second messenger function. It has a kind of postsynaptic effect.

Another approach is to **enhance GABA function with an anticonvulsant**.

In rats **BDNF** seems to improve the depressed state.

There is a **delayed onset of action of antidepressants**. This makes patient compliance difficult because the patient is usually pessimistic about everything including treatment. Patients become convinced that nothing will work especially after they are told that treatment is not going to work for a couple of weeks. It is unclear why there is this delayed onset of action.

One of the reasons that SSRIs take a long time to work might be related to the 5-HT1A auto receptors. The first thing that happens when serotonin increases is that it binds the 5-HT1A receptors, which shuts down the serotonergic neuron. Consequently, the amount of gain in serotonergic activity if it is present is reduced dramatically by these auto receptors. However, through mechanisms not yet understood, the **5-HT1A receptors become desensitized and lose their ability to provide feedback inhibition on the serotonin system**. They progressively desensitize over a period of weeks and as they are desensitized the firing of the serotonin neuron and the amount of serotonin released gradually increases. Therefore, SSRIs work better with increased time. SSRIs block reuptake, but if there is not much serotonin to begin with there is little effect. The more serotonin the more the effect of blocked reuptake.

There are **effects beyond the neurotransmitter** at the second messenger level (e.g. ECT has a particular effect in enhancing second messenger systems and some norepinephrine neurotransmitter targeting agents do the same thing). Lithium interestingly has an anti manic action and one of its effects is to dampen down certain postsynaptic effects. And many antidepressants seem to enhance BDNF and perhaps encourage brain growth.

There are some treatments that take advantage of the fact that certain peptides are in excess (e.g. CRH and substance P in stress systems). Antagonists that block these peptides are being used as antidepressants. Successful treatment will tend to normalize the HPA stress system's hyperactivity. Very often when patients start to get better the hyperactivity of the HPA system will begin to drop. If a **CRH antagonist** is given the HPA system shuts down completely and patients get better. It is believed that **too much CRH is actually a depressant**. Remember that **hyperactivity of the CRH system may be pathogenic**. It has been found that the greater the time individuals have gone untreated the smaller the hippocampus. It is believed that shutting off the HPA axis and the corticosteroids will relieve some of the brain shrinkage that occurs in depression. **Antidepressant treatment may actually have a pro-growth effect on the brain**.

Summary:
It is important to diagnose and treat depression because without treatment people's lives suffer enormously (e.g. social and family relationship damage, problems with school failure, job loss, financial dependence). **60% of all suicides are in the context of a mood disorder**. There may actually be brain cell loss or even cell process retraction and atrophy when people are not treated, and this might be reversible through treatment.