Theories of Depression

by Richard H. Hall, 1998

Monamine/5-HT Hypothesis

Just as with schizophrenia, the most popular neurophysiological theory of depression follows from the drugs that are used to treat it. The evolution of antidepressant drugs has, in some ways, been the systematic narrowing down of monoamines to Serotonin. MAO inhibitors are Dopamine-Epinephrine-Norephinephrine-Seratonin agonists. Tricyclic Antidepressants are Norepinephrine-Serotonin agonists, and, finally SSRIs act as Serotonin (5-HT) agonists. Thus, the monoamine hypothesis has evolved in the same way, so that today one popular theory of depression, the **Monoamine Hypothesis**, is that depression is the result of underactivity of monoamines, especially 5-HT. Besides the fact that antidepression drugs are all monoamine agonists, there is other evidence that supports the theory. First, **Reserpine**, a monoamine *antagonist*, which was used to treat things like high blood pressure, is rarely used at the present time due to the fact that depression is a common side effect. Thus, not only can monoamine agonists decrease depression, but monoamine antagonists (Reserpine) can induce depression. Another piece of evidence in support of the Monoamine Hypothesis is that levels of 5-HT, as measured by its metabolites, seem to be correlated with depression. For example, patients who have low levels of a 5-HT metabolite were found to be more likely to have committed suicide.

It often takes two to three weeks for antidepressant drugs to effectively treat depression. This is a difficult phenomenon to explain within the context of the monoamine hypothesis. Presumably, in response to monoamine agonists these neurotransmitter levels increase right away, and, if depression is caused by low levels of the neurotransmitter, then depression should decrease as the levels of monoamines increase. Two contrasting theories have been offered to explain this puzzling phenomenon, both of which rely on the supposition that the nervous system will compensate for large fluctuations in neurotransmitter levels with a compensatory increase or decrease in neurotransmitter or receptor release or sensitivity. The first theory is the straightforward contention that the important effect of the antidepressant drugs is exactly the opposite of what the monoamine theory suggests. That is, over the course of three weeks the 5-HT post-synaptic receptors become **subsensitive** (as contrasted with the supersensitivity discussed in a schizophrenia module), so that the neurons actually become less responsive to 5-HT as a result of the antidepressants. Depression then, according to this interpretation is the result of the *overactivity* of 5-HT neurons, and after the 5-HT agonists are taken for some time the 5-HT neurons respond less and less, and the depression goes away as a result.

A second theory for this time-lag effect has now become more widely accepted, which is *consistent* with the monoamine hypothesis that depression is due to underactivity of 5-HT neurons. However, this theory still relies on the concepts of neural compensation and subsensitivity. The crucial difference is that according to what we'll call **the autoreceptor subsensitivity theory**, it is not the post synaptic receptors that become subsensitive, rather it is 5-HT autoreceptors. **Autoreceptors** are typically located on the presynaptic or axonal membrane. These receptors, which serve a feedback function, are sensitive to the amount of neurotransmitter present in the intercellular fluid, and have an inhibitory effect on neurotransmitter production and/or release. Presumably, the initial effect of the monoamine

agonists is to stimulate these autoreceptors such that they inhibit the increased release of monoamines resulting from the drug. After two or three weeks, however, the autoreceptors become subsensitive due to continued stimulation, and quit sending their inhibitory signal, so the monoamine agonists then have the effect that we would expect. (Figure 1 illustrates the contrast between the post-synaptic and autoreceptor subsensitivity hypotheses).

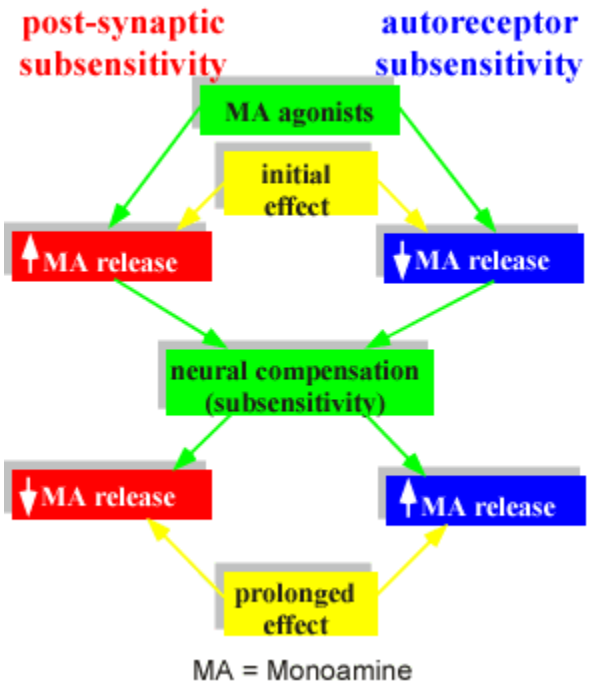

Figure 1. Post-Synaptic vs. Autoreceptor Subsensitivity Hypotheses of Depression

Circadian Rhythms

Another theory of depression also follows from successful treatment. The fact that sleep deprivation can effectively treat depression has lead some to the conclusion that abnormal sleep patterns may play a role in depression. Also, most antidepressant drugs decrease or eliminate REM sleep, and those who suffer depression have been found to have abnormal sleep cycles. More specifically they have more REM, a shorter onset until REM, and generally more disrupted cycles. Finally, those who have been successfully treated with sleep deprivation, will often revert back to their depressed state as a result of a short nap. This has even lead some to suggest that some type of **depressogenic** substance is released during sleep, and that the substance is deactivated during wakefulness. In fact, a typical pattern for some diagnosed with a major depression disorder is for the perception of depression to peak in the morning and decrease as the day goes one, which would be consistent with the idea that such a substance was being depleted as the day progresses.