Moving Beyond the Monoamine Hypothesis to Examine the Fundamental Difference in Endocrine Function between Depressed Patients and Normal Patients and Differences in the Physiological Mechanism

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According to the DSM-IV-TR, a depressive disorder is an “illness that involves the body, mood, and thoughts.” It affects the way a person carries out the necessary functions of life, like eating or sleeping, the way a person feels and thinks about themselves and about the world at large. A depressive disorder is not the same as a transient feeling of sadness. It is in no way an illness of the weak, and it is not something that can merely go away upon whim or intense will. Without treatment, symptoms can last for weeks, months, or years. Appropriate treatment, however, can help most people who suffer from depression (DSM-IV-TR, 2000).

The symptoms of depression include “depressed mood most of the day, nearly every day, as indicated by either subjective report or observation made by others,” “feelings of worthlessness or excessive or inappropriate guilt,” “insomnia or hypersomnia nearly every day,” “decrease or increase in appetite nearly every day,” “diminished ability to think or concentrate, or indecisiveness,” “recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan,” “loss of interest or pleasure in hobbies and activities that were once enjoyed, including sex” and “psychomotor agitation or retardation nearly every day” (DSM-IV-TR, 2000). In severe cases, delusions and hallucinations may be present.

Patients exhibiting the symptoms of depression are generally suffering from clinical depression. The term major depression describes a depressed state characterized by several symptoms that last chronically for at least 2 weeks. Dysthymia is characterized by less severe symptoms that last much longer, at least 2 years. Both of these types of depressive disorders occur in the absence of other psychological or physical problems and are considered primary depression. Secondary depression refers to depression that results from some other physiological

or psychological dysfunction. Individuals who are depressed for a transient period of time because of some clearly identifiable stressor or environmental stimulus are said to be suffering from bereavement reactions (DSM-IV-TR, 2000). The bouts of depression in these individuals are short-lived, and these individuals fully recover without treatment. Depression is considered to be at an extreme in the mood continuum, and depressed individuals usually vary in the severity and the duration of their symptoms. The prevalence of depressive symptoms is determined by means of psychological tests such as the Hamilton rating scale, as will be seen in the following studies.

The most popular neurophysiological theory of depression follows from the drugs that are used to treat it. Monoamine oxidase (MAO) is produced by all monoamine neurons and functions to dominate these neurotransmitters in the terminal button. Therefore, the amount of monoamine available for storage and release is regulated by MAO. MAOIs prevent this oxidative reaction, resulting in increased availability of the neurotransmitters for storage and release. There are two subtypes of MAO that preferentially deaminate different monoamines: Monoamine oxidase-A deaminates norepinephrine, dopamine and serotonin, while Monoamine oxidase-B deaminates dopamine and phenylanine but has less specificity for norepinephrine and serotonin. The early MAOIs inhibited MAO-A and MAO-B equally, but newer MAOIs are typically irreversible, meaning that once they deactivate MAO, the enzyme remains unavailable in the terminal button until it has been replaced. The resynthesis of MAO may take as long as several weeks. As with the tricyclic antidepressants, the lag time from initial treatment to the observation of therapeutic effects is typically about two weeks (Ettinger, 2011). Tricyclic antidepressants are norepinephrine-serotonin agonists, and selective serotonin reuptake inhibitors

(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. The antihypertensive drug reserpine binds to the vesicular transporter protein, preventing newly synthesized or recycled monoamine neurotransmitters such as catecholamines and serotonin from being transported into synaptic vesicles. Neurotransmitter remaining in the terminal button is quickly degraded by MAO. Reserpine nonselectively antagonizes dopamine, norepinephrine, by depletion, producing behavioral depression and sedation (Ettinger, 2011). 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. Thus, selective serotonin reuptake inhibitors (SSRIs) were developed specifically to inhibit the reuptake of serotonin by competitively binding without the serotonin transporter protein. This competitive binding effectively blocks the reuptake of a significant amount of extracellular serotonin leaving it available to engage pre- and postsynaptic receptor sites for longer durations. It is believed that the antidepressant effects of SSRIs are mediated primarily by the 5-HT1A receptor types while some of their adverse side effects may be mediated by 5-HT2 receptors. Specifically, the 5-HT1A autoreceptor is believed to be overexpressed in major depression, resulting in excessive inhibition of serotonergic neurons in the raphia nucleus, amygdala, and the hippocampus.

Chronic treatment with SSRIs leads to downregulation of these inhibitory autoreceptors and a corresponding increase in serotonergic activity. (Ettinger, 2011)

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. However, there is a time lag which is a tremendous problem when there are cases of suicide patients.

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:

> "As well as the distressing symptoms of sleep disturbance experienced by patients, changes in objective sleep architecture are well-documented in depression. Compared with normal controls, sleep continuity of depressed subjects is often impaired, with increased wakefulness (more frequent, and longer periods of wakefulness), and reduced sleep efficiency. Sleep onset latency is significantly increased and total sleep time reduced. Rapid eye movement (REM) latency is often shortened, and the duration of the first REM period is increased. The number of eye movements in REM (REM density) is also increased." (Nutt et al., 2008)

Most antidepressant drugs decrease or eliminate REM sleep, and those who suffer depression have been found to have abnormal sleep cycles and that the neurotransmitters being targeted by current antidepressants play important roles in the sleep/wake cycle (Winokur et al.,

2001). By inhibiting both the serotonin and norepinephrine transporters, SNRIs engage a broader mechanism of action than do SSRIs. Venlafaxine is the only currently available drug in the SNRI category. In addition to inhibiting presynaptic uptake of 5-HT, venlafaxine also exhibits some potency in inhibiting dopamine uptake. Luthringer et al. (1996) did report that venlafaxine at doses of 75 to 375 mg per day inhibited serotonin, norepinephrine and dopamine. Depression and antidepressant drugs are known to modify human sleep patterns. A double-blind, placebo-controlled study was conducted to assess the effects of venlafaxine and the placebo on sleep (through EEG spectral analysis) and clinical measures (Hamilton Rating Scale for Depression) in patients with major depression. Following a two-week placebo washout period, patients were randomly assigned to receive either placebo or venlafaxine for up to 29 days. Sleep evaluations took place at baseline (3 nights immediately before entering the double-blind phase), after 1 week of treatment, and after 1 month of treatment. The results showed improvement from baseline in both treatment groups at all time points, with improvement tending to be greater in the venlafaxine group. Venlafaxine induced a decrease of sleep continuity (decreased total sleep time and increased wake time), an important increase in the onset latency of rapid eye movement (REM) sleep, and a decrease in total REM sleep duration. (Luthringer et al., 1996)

The final theory of depression addressed the previous theory of depression in that the patients have seen successful results with the effects of sleep deprivation on their depression, but will feel depressive symptoms shortly after a small bout of sleep. This could probably be due to increasing irregularities in sleep patterns (Conner, Psy. D, Oregon Counseling) or that a specific substance with depressive properties is released during sleep, peaks in the morning, and decreases throughout the day. This would consistent with the idea that the substance in question,

a hormone, was lessening or being expelled as time passed. However, it is unclear whether depression causes changes in hormone production or whether changes in hormone production cause depression. Thus, several endocrine correlates will be examined.

The hormones of the hypothalamic-pituitary-thyroid axis have been implicated in depression (Musselman and Nemeroff, 1996):

> "In response to stress, hypothalamic neurons containing corticotropin-releasing factor (CRF) increase synthesis and release of corticotropin (ACTH), b-endorphin, and other pro-opiomelanocortin products from the anterior pituitary gland. Many studies have documented evidence of hypothalamic-pituitary-adrenocortical axis hyperactivity within medication-free patients with major depression, ie, elevated CRF concentrations in cerebrospinal fluid, blunting of the ACTH response to CRF administration, nonsuppression of cortisol secretion."

Administration of thyrotropin-releasing hormone (TRH) stimulates the release of thyroid-stimulating hormone (TSH) from the anterior pituitary gland and subsequent hormone production by the thyroid gland. Administration of TRH to depressed individuals has been attempted in several studies. In one such study, five patients who were mentally depressed received thyrotropin (TSH) and thyrotropin releasing hormone (TRH) for 3 days as part of a double-blind, cross-over study. All patients showed improvement in the symptoms of depression. The plasma-TSH response to TRH was distinctly diminished in four of the five patients, suggesting an abnormality in the hypothalamic/pituitary axis, which was an extremely unusual finding given that the patients did not have any thyroid disfunction.

The depressive symptoms of PMS have also been associated with thyroid function. In one study, the responses of TSH and prolactin concentrations to TRH administration were examined in women who reported PMS symptoms and in women who did not. PMS patients reported rates of depression from 45% to 60%. TRH had been found to stimulate prolactin release in women who weren't depressed, but did not affect prolactin levels in depressed women (Roy-Byrne et al., 1987). TRH was given during both the follicular and luteal phases. There were no significant differences in basal or maximal elections of TSH or prolactin in response to the treatment between women with and without PMS symptoms, and neither TSH nor prolactin values differed between the luteal and follicular phases. However, the women with PMS showed much greater variation in TSH response to TRH treatment than the control women' that is, sometimes TSH levels were augmented, but at other times they were reduced (Roy-Byrne et al., 1987). Women without PMS showed stable responses of TSH to TRH. Variable TSH response to TRH could be present in a subgroup of women that suffer depression as part of their PMS symptoms.

Growth hormone (GH) concentrations have been reported to be in the normal range in depressed patients. However, impaired GH responses to insulin-induced hypoglycemia in depressed patients have been reported by Brunswick et al (1988). The study examined the pretreatment growth hormone response to insulin in 132 depressed patients and 80 healthy controls. It was found that depressed patients, either unipolar or bipolar, showed less of a fall in glucose than controls, and that there was a weak correlation between the magnitude of the fall in glucose and the severity of the depression. Gender was not determined to be a confound in the differences found in values for the unipolar or bipolar depressed patients.

These studies all point a fundamental difference in endocrine function between depressed patients and nondepressed patients and suggest differences in the physiological mechanism underlying their endocrine feedback control systems.

The negative feedback features of the hypothalamic-pituitary-adrenal (HPA) axis appear to be impaired in depressed patients. According to Maes et al. (1994) it is usually said that about 50% of patients with major depression hypersecrete cortisol. Normally, it's present in the body at higher levels in the morning, and at its lowest at night. Although "stress isn't the only reason that cortisol is secreted into the bloodstream, it has been termed 'the stress hormone' because it's also secreted in higher levels during the body's 'fight or flight' response to stress, and is responsible for several stress-related changes in the body," (Scott, 2011). These increased serum cortisol concentrations do no appear to reflect the stress of coping with depression, because cortisol concentrations in depressed patients are at their highest 3-4 hours after sleep onset, when stress levels should be lowest, and decrease throughout the daylight hours, when stress levels are presumably highest. Fang et al. (1981) conducted a study to examine plasma ACTH and cortisol levels in depressed patients by collecting blood samples from normal subjects and depressed patients to monitor ACTH and cortisol levels in the morning on the day before receiving dexamethasone and the morning and afternoon on the day after receiving dexamethasone. It was found that the mean plasma ACTH values of these two groups were not significantly different at any of the times, while the cortisol levels of the depressed patients were significantly higher than those of the normal subjects in the morning pre-dexamethasone. Because cortisol is normally secreted in a pronounced circadian pattern, with peak patterns measured in the early morning, this disturbance of the diurnal rhythm of

cortisol secretion in depressed patients suggest an abnormal disinhibition of the neural centers regulating the release of ACTH.

Works Cited

1. American Psychiatric Association. (2000). Diagnostic and statistical manual of mental disorders (4th ed., text rev.). Washington, DC: Author.

Brunswick, D., Frazer, A., Koslow, S., Casper, R., Stokes, P., Robins, E., et al. (1988). Insulin-induced hypoglycaemic response and release of growth hormone in depressed patients and healthy controls.. *Psychol Med.*, *18*(1), 79-91.

2. Conner, M. G. (n.d.). Understanding And Dealing With Depression (ages 6 to 12 yrs. old). *Oregon Counseling, Psychotherapy, Counseling, Therapy, Information,Education, Referral, Research*. Retrieved December 22, 2012, from http://www.oregoncounseling.org/handouts/depressionchildren.htm

3. Ettinger, R. H. (2011).*Psychopharmacology*. Upper Saddle River, NJ: Prentice Hall.

4. Fang, V. S., Tricou, B. J., Robertson, A., & Meltzer, H. Y. (1981). Plasma acth and cortisol levels in depressed patients: Relation to dexamethasone suppression test. *Life Sciences*, *29*(9), 931-938.

5. Luthringer, R., Toussaint, M., Schaltenbrand, N., Bailey, P., Hackett, D., Guichoux, J., et al. (1996). A double-blind, placebo-controlled evaluation of the effects of orally administered venlafaxine on sleep in inpatients with major depression.. *Psychopharmacol Bull.*,*32*(4), 637-46.

6. Maes, M., Calabrese, J. & Meltzer, H. Y. (1994) The relevance of the in-versus outpatient status for studies on HPA-axis in depression: spontaneous hypercortisolism is a feature of major depressed inpatients and not of major depression per se. Progress in Neuropsychopharmacology and Biological Psychiatry, 18, 503-517

7. Musselman, D. L., Evans, D. L., & Nemeroff, C. B. (1998). The Relationship of Depression to Cardiovascular Disease. *Arch Gen Psychiatry*, *55*, 580-592.

8. Nutt, D., Wilson, S., & Paterson, L. (2009). Sleep disorders as core symptoms of depression. *Dialogues Clin Neurosci*, *10*(3), 329-336.

9. Roy-Byrne, P., Rubinow, D., Hoban, M., Grover, G., & Blank, D. (1987). TSH and prolactin responses to TRH in patients with premenstrual syndrome. American Journal of Psychiatry, 144 (480), All.

10. Scott, E. (n.d.). Cortisol and Stress: How Cortisol Affects Your Body, and How To Stay Healthy in the Face of Stress. *Stress and Stress Management - Causes, Symptoms, Stress Relief Tips and Stress Tests*. Retrieved December 22, 2012, from http://stress.about.com/od/stresshealth/a/cortisol.htm

11. Winokur, A., Gary, K. A., Rodner, S., Rae-Red, C., Fernando, A. T., & Szuba, M. P. (2001). Depression, Sleep Physiology, and Antidepressant Drugs.*Depression and Anxiety*, *14*, 19-28.