

# **Clinical Depression: Chemical Imbalance and Dying Cells**

by Maryna Stavvytska- Barba

## **Introduction**

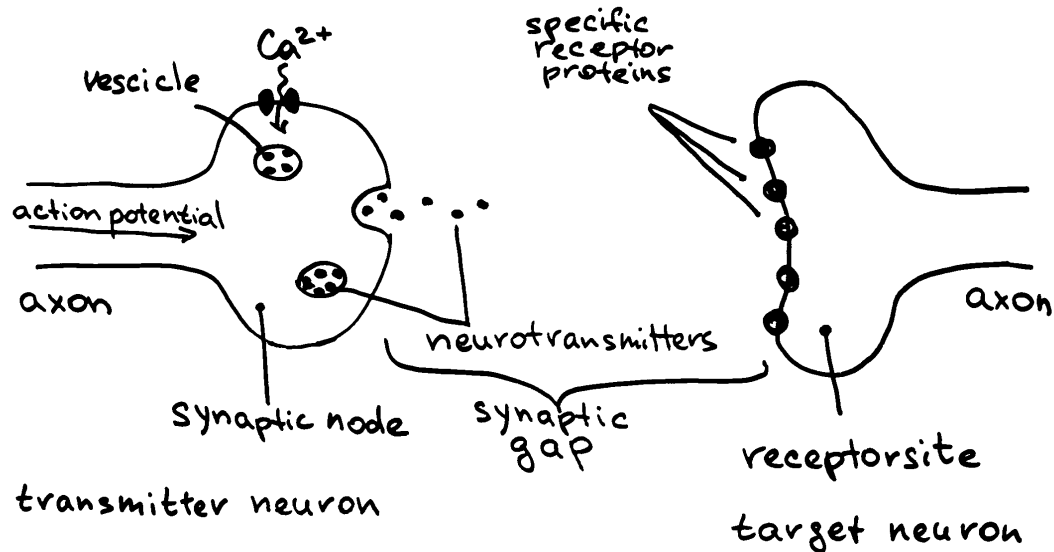
Major Depressive Disorder is the leading cause of disability in the U.S. for ages 15- 44.<sup>1</sup> This bold and impressive statement is more than enough for us, as a society, to turn our heads, to stop and to think how we can change the statistics and how we can lessen this practically epidemic disorder. In other words, approximately 14.8 million American adults, or about 6.7 percent of the U.S. population age 18 and older in a given year, have a major depressive disorder.<sup>2</sup>

As defined by the National Institute of Mental Health, depression is a serious medical condition. In contrast to the normal emotional experiences of sadness, loss, or passing mood states, clinical depression is persistent and can interfere significantly with an individual's ability to function.<sup>3</sup> There are many different possible causes of depression proposed: genetic predisposition<sup>4</sup>, stressful life events<sup>5</sup>, chemical imbalance<sup>6</sup> or physiological disfunctions<sup>7,8</sup>. Perhaps one of them is solely correct, or perhaps their combinations trigger the development of depression, but in any event, the result is a gloomy depression that needs to be fully understood to be effectively treated. Insight into better understanding and possible treatments of clinical depressions is a goal of this biochemical review.

## **Chemical imbalance theory**

Information is passed by a chain of neurons

The oldest theory about depression that was proposed by Schickraut in 1965 links depression with a chemical imbalance of neurotransmitters between neurons in the brain. It was proposed on the basis of recognizing the relationship of izoniazid and reserpine and neurotransmitter levels<sup>6</sup>. A modified version of how neurotransmitters work was found in *Human Physiology* by Stuart Ira Fox. The neurotransmitters are regulatory molecules that are released from the synaptic node of transmitter neurons and receptors on target neurons (figure 1).



**Figure 1**

When the neural impulses are sent through neurons as electricity, it is said that an action potential travels through them. An action potential that reaches the synaptic node of one neuron can not jump to the next one through the synaptic gap. Neural cells use a special kind of mechanism.

When the action potential reaches the synaptic knob, then the membrane of a transmitter neuron is depolarized, therefore voltage-gated calcium ion channels open. Calcium from outside of the cell enters and binds to the vesicles which contain neurotransmitters. This causes the vesicles to fuse with the membrane of the cell at the synaptic node “spilling” neurotransmitters into the synaptic gap. Some of those neurotransmitters reach the target neuron’s membrane and interact with specific receptor proteins. In a case of monoamine neurotransmitters, along with these neurotransmitters intermediate regulators (AKA second messengers) arrive to the same specific receptor proteins from the receptor site of the target neuron.<sup>21</sup> Together, neurotransmitters and intermediate regulators, cause ion channels to open in the target neuron and membrane polarization occurs, so that action potential will travel through the target neuron as well. An example of such second messenger is an earlier discussed Calcium.

If there are not enough neurotransmitters reaching specific receptor proteins, then less ion channels will open. If there are not enough ion channels open, then an action potential might not fire at all (it either fires at full force or does not fire at all), and then initial information communicated to the first neuron is lost and not delivered. This loss of information is pathophysiologically linked to depression.

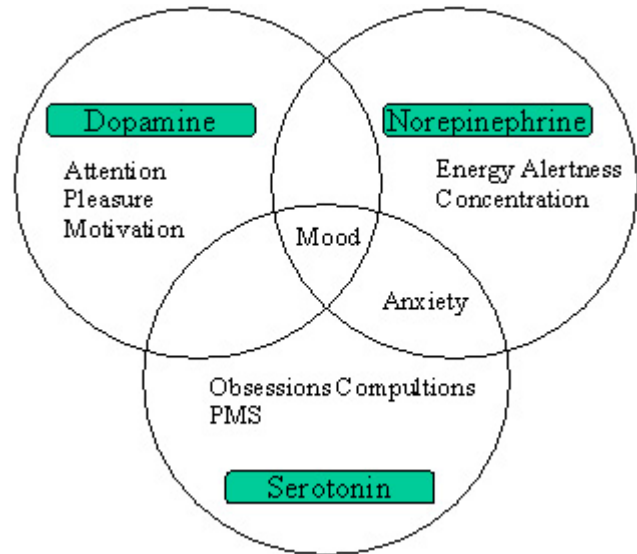
There are three reasons why sometimes there are not enough neurotransmitters that reach specific receptor proteins. First reason is due

to enzymatic (monoamine oxidase) degradation of neurotransmitters in the synaptic nodes. The second reason is due to augmented reuptake of neurotransmitters by the terminal button (some reuptake is supposed to happen). The third reason is due to enzymatic (catechol- O- methyltransferase) degradation of neurotransmitters at the target neuron and in the synaptic gap.

Therefore, according to the chemical imbalance hypothesis, if any one of the above factors that diminish neurotransmitter levels are decreased, then the neurons should deliver more information, and therefore depression should lessen.

Different neurotransmitters have different functions

There are three major types of neurotransmitters in the body: **amino acids** (glutamic acid, GABA, aspartic acid and glycine, etc.), **peptides** (vasopressin, neurotensin ,somatostatin, etc.) and **acetylcholine and monoamines** (norepinephrine, dopamine and serotonin). Major neurotransmitters of the brain are the amino acids (glutamic acid and GABA), but they are considered to be non-essential since they are simply synthesized in the brain. Peptides are the neurotransmitters in the hypothalamus which is located prior to blood-



**Figure 2**

dopamine and serotonin). Major neurotransmitters of the brain are the amino acids (glutamic acid and GABA), but they are considered to be non-essential since they are simply synthesized in the brain. Peptides are the neurotransmitters in the hypothalamus which is located prior to blood-

brain barrier\*. There are comparatively few acetylcholine receptors in the brain (the effects of acetylcholine is considered to be more important in muscles). Considering all of the above, researchers tend to concentrate their studies on monoamines as neurotransmitters in the brain.

Monoamines are thought to perform specialized modulating functions in the brain\*\*. Also monoamines are major neurotransmitters that are thought to play a role in mood regulation, cognition and behavior<sup>6</sup> (Figure 2).

---

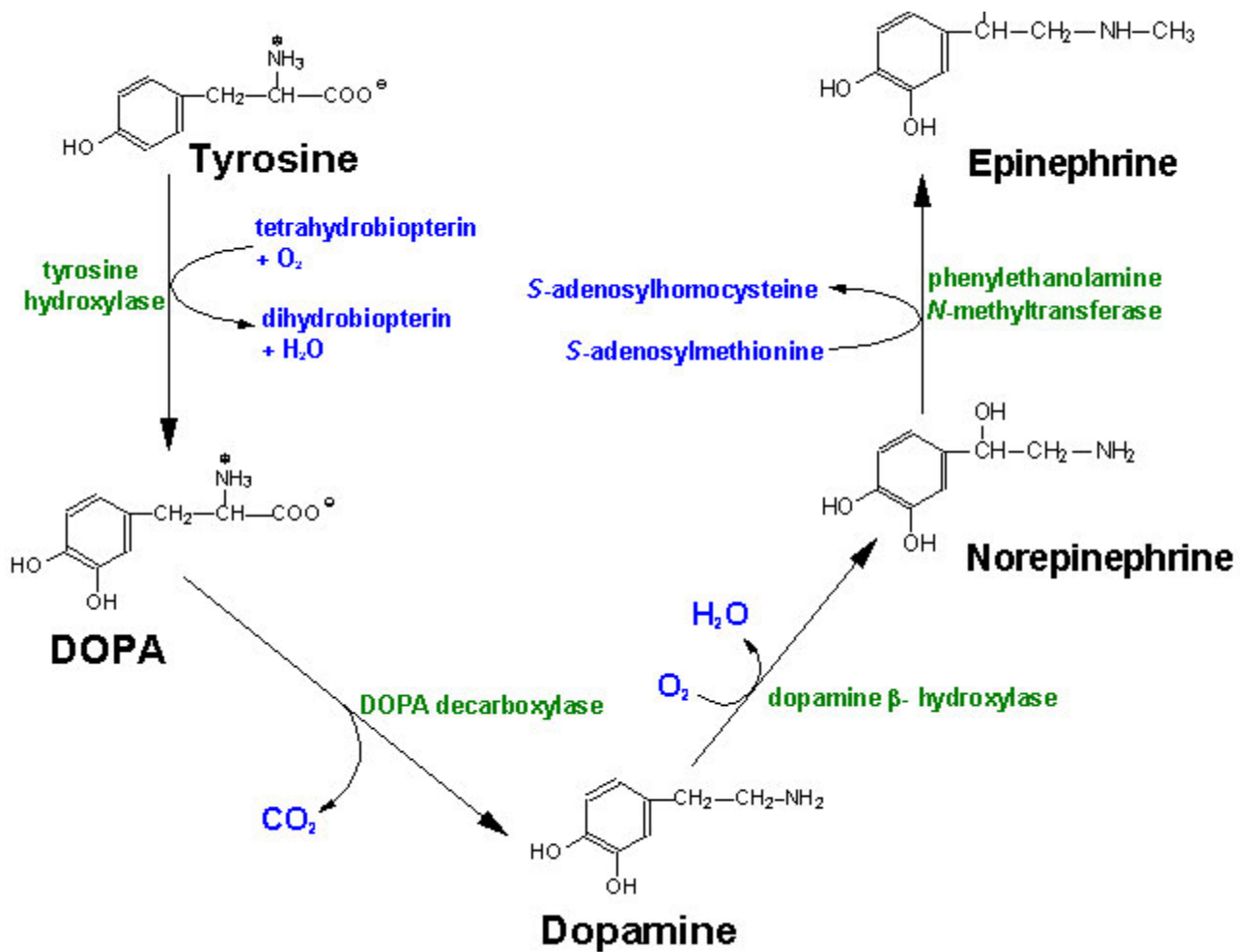
\*The blood- brain barrier is a semi- permeable endothelial cell layer which forms a membrane that controls the passage of substances. Some molecules can travel through it: lipid soluble water, oxygen, carbon dioxide, ethanol and steroid hormones; small electrolytes; molecules allowed in by specific transport systems (such as sugars and some amino acids). Molecules with a molecular weight higher than 500 Daltons usually can not pass through the blood- brain barrier; however some large molecules can be transported through if they are specifically carried by transport proteins. Blood- brain barrier creates a chemical environment in the brain where molecules can carry out functions independent of the functions they carry in the rest of the body. For example, peptides can not be transported across the blood- brain barrier. Amino acid neurotransmitters in the brain are synthesized behind the blood- brain barrier instead of being transported. Monoamine levels in the brain are also independent of their concentrations in the rest of the body.

\*\*Modulating functions of the brain are the once that a response in the body where sensory functions do not. The examples of modulating functions of the brain of are emotion, blood pressure, mood, pain, appetite, sexual motivation, alertness and the neuroendocrine system.

### Catecholamine neurotransmitters

Dopamine and norepinephrine are catecholamines and are derived from tyrosine that was not incorporated into protein synthesis and not

catabolized for energy. Tyrosine is transported to the neurons that have to secrete catecholamines for catecholamine synthesis (Figure 3).



### Figure 3

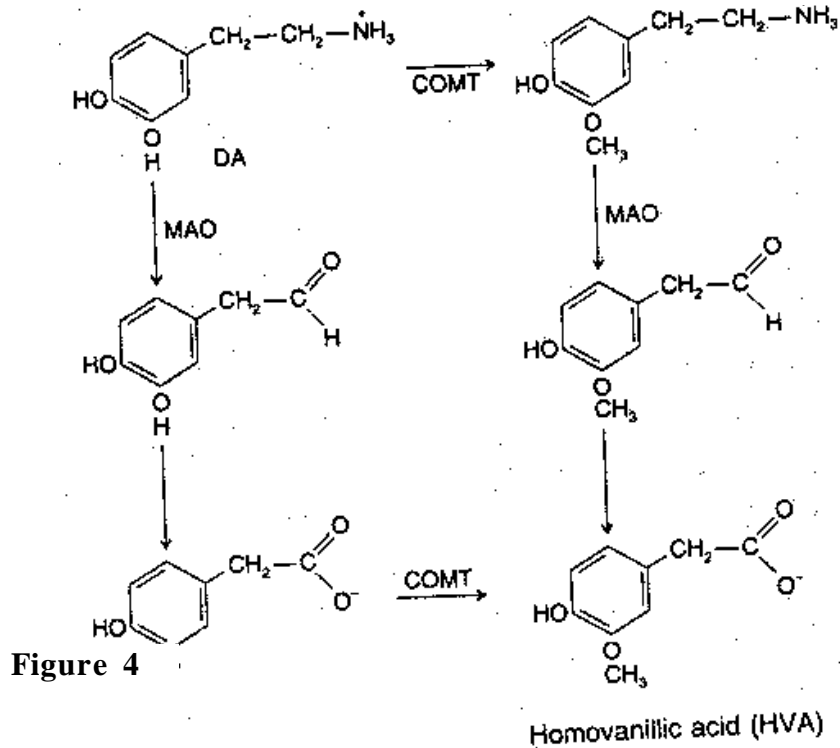
Lack of dopamine is thought to play a role in depression. Medicine that causes production of dopamine is used when other measures have failed to treat a depression because a high concentration of dopamine can cause psychosis. This kind of medicine gives inconsistent results in different people, therefore it is considered to be the last resort.

Schildkraut proposed that deficiency of norepinephrine causes depression <sup>6</sup>. However, the decrease in norepinephrine does not cause depression consistently in all people. Therefore, medicine that targets an increase in norepinephrine does not produce consistent results and should be reserved as a last resort.

Dopamine and norepinephrine can be metabolized by a two- step process through catecholamine- O- methyltransferase (COMT) and monoamine oxidase (MAO) (Figure 4). Active COMT is found in the synapses, and uses S-Adenosyl Methionine (SAM) as a methyl- group donor. MAO is found in nerve endings and it does not enter synapses; MAO catabolizes catecholamines that are not securely enclosed into vesicles. Since neither neurotransmitter (dopamine or norepinephrine) stays in a synaptic cleft as long as it stays in the synaptic node, MAO accounts for larger neurotransmitter degradation than COMT does. In other words MAO has more potential time when it can catabolize the catecholamines. Since drugs that inhibit MAO are considered to be more effective against

depression, there are more drugs that are designed to inhibit MAO and not COMT.

Also it is worthy to note that antidepressant drugs are designed to inhibit MAO-A type. MAO-A is an isozyme that metabolizes norepinephrine, dopamine and serotonin. Most MAO-A inhibitors are hydrazine derivatives which are highly reactive and form a strong covalent bond with MAO-A and therefore inhibits it. However, in the brain, a majority of MAO is MAO-B type and it is not effected by MAO-A inhibitors. (MAO-B metabolizes the neurotoxin MPTP to its active form and it metabolizes phenylethylamine and dopamine to some extent).



The drugs that inhibit neurotransmitter re-uptake are named tricyclic anti-depressants (see Figure 5 for examples). Desipramine inhibits norepinephrine reuptake. Imipramine and amitriptyline inhibit norepinephrine and serotonin reuptake. If the reuptake of neurotransmitters is inhibited, then neurotransmitters continue to stimulate the target neuron, and the neurons deliver more information.

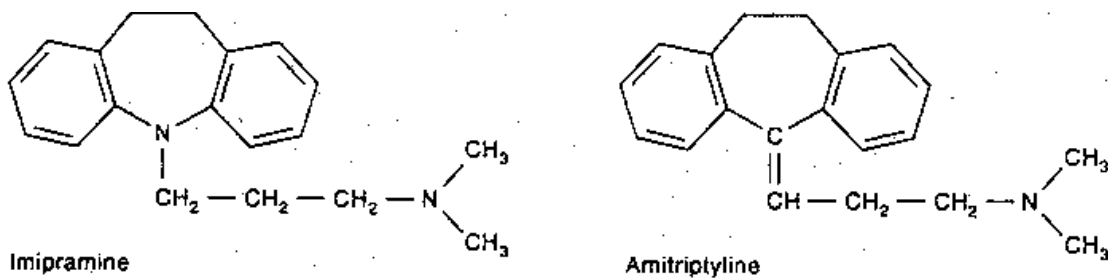
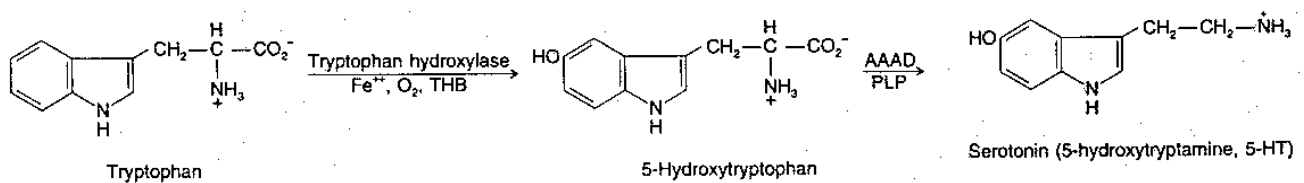


Figure 5

### Indolamine neurotransmitter

Serotonin is the indolamine neurotransmitter synthesized independently in the brain and in the rest of the body. It is synthesized out of tryptophan (Figure 6). Virtually all tryptophan in the brain is converted to serotonin. (In contrast, only leftovers of tyrosine that are not incorporated into protein synthesis are used to synthesize



catecholamines). Also tryptophan is very scarce amino acid. As a result, amounts of serotonin in the brain are very sensitive to the diet.

Low levels of serotonin increase anxiety, obsessions and impulsive behavior. For example, monkeys with low levels of serotonin but high levels of testosterone lack restraints and are aggressive. Experimentally exposed to lead, monkeys become very aggressive (lead interferes with serotonin release into the synapses because it interferes with serotonin synapse development)<sup>9</sup>.

Serotonin reuptake can be lowered by serotonin specific reuptake inhibitors (SSRI) such as Prozac. SSRI are currently the medicine of choice to fight depression. Also MAO- A inhibition can be used to increase the concentration of serotonin since MAO- A is an isozyme that metabolizes norepinephrine, dopamine and serotonin (as described previously).

Important detail: MAO inhibitors and tricyclic antidepressants have immediate effects on brain monoamines, however, clinical antidepressants require several weeks of administration before they produce a therapeutic effect. Chemical imbalance theory fails to explain this phenomenon.

### **Dying cells theory**

#### Beyond Serotonin

New ground- breaking research was done by Mark Mintun and Yvette Sheline<sup>10</sup>. Positron emission tomography (PET) was used to analyze the binding of serotonin to a serotonin <sub>2A</sub> receptors. The analysis of the kinetic assay data showed that the binding was reduced by 29% on average in the

hippocampus in depressed subjects in comparison to a closely matched control group of women. They also noticed smaller size of the hippocampus (up to 15% smaller measured with PET) in the women with depression. The longer the women had depression, the smaller their hippocampi were.

Similar conclusions were made by McEwen with his experiments on mice: due to induced stress by physical restraining them, the adrenal gland in these mice was stimulated to release cortisol<sup>11</sup>. With time, cortisol damages the brain by degrading the dendrite endings or killing cells completely, decreasing the size of hippocampus. Hippocampus and amygdala are the parts of a limbic system. Amygdala regulates emotions and triggers response to danger. Hippocampus is involved in learning, memory and emotion (since it is connected to amygdala), therefore it might contribute to depression.

Also with magnetic resonance imager scans of brains, it was found that amygdala (which is responsible for generating unpleasant emotions) was active when unpleasant pictures were shown to tested humans<sup>12</sup>. After a few seconds, the left prefrontal cortex would become more active in healthy individuals, where in depressed individuals right prefrontal cortex would stay more active<sup>13</sup>. Also, researchers found that if the left prefrontal cortex becomes active, not only will an individual's emotional state improve, but cortisol levels become lower.

Another group of researchers analyzed samples of amygdalas from depressed and not depressed individuals (the diagnosis of their state was made from interviews of relatives or psychiatrists)<sup>14</sup>. They have found that the number of neurons did not get smaller, but there were less glial cells. Glial cells stabilize levels of neurotransmitter glutamate, package dead cells to be taken away, and provide a supply of glucose to neurons (blood glucose enters the glial cells that are attached to the capillaries; then the glucose is partially metabolized; and then it is sent to the neurons).

### Neuronal Plasticity

These discoveries indicate that there is not only a change in neurotransmitters' chemistry, but there are greater changes that take place. It was recognized, though, that medicine that affects neurotransmitters does aid with depression. Many psychiatrists noted that even though serotonin reuptake inhibitors increase neurotransmitter levels within hours, it takes couple of weeks to help with a depression. Richard Duman was the first one to propose the theory of how the neurotransmitters help to relieve the depression.<sup>15</sup>

Duman found that nerve cells of depressed individuals have a deficit in brain- derived neurotrophic factor. Also he found that effective antidepressants not only increase levels of serotonin in the synaptic clefts and help signals travel more efficiently, but that effective antidepressants increase levels of brain- derived neurotrophic factor in hippocampus.<sup>15</sup> (The levels were determined ex vivo after administering antidepressants;

BDNF protein were measured using ELISA, enzyme-linked immunosorbent assay; serotonin levels were measured using HPLC-EC instrument and Beer's Law). Initially Duman thought of brain-derived neurotrophic factor as a specific nerve growth factor that helps the neuron of the brain to sprout new dendrite spines and open new neural pathways in the brain.<sup>15</sup> Now the brain-derived neurotrophic factor is identified with sustaining and protecting neurons in adult brain as well as with neurogenesis, "birth" of new neurons. Elizabeth Gould proved Duman's thought by labeling newly formed neurons that were generated from dividing cells in the dentate gyrus of adult humans. To label the new cells, the bromodioxuridine was administered intravenously in high concentrations so that some of it would pass through the blood-brain barrier; bromodioxuridine is then taken up into dividing cells and later it can be detected by staining. This was done on mice that were euthanized later, and on humans who were in the late stages of progressing cancer. In both cases, new neurons were detected in the brain (in the case of humans with cancer it was extra special since they were going through great deals of stress).

There is no solid theory on how the neurogenesis happens yet, there are only hypotheses. Therefore, new researches should focus on exploring the mechanisms of neurogenesis and on finding more medicine that will rejuvenate the non-working cells, and not on overloading the existing ones.

## Conclusion

Chemical imbalance theory links depression with a chemical imbalance of neurotransmitters between neurons in the brain due to not enough neurotransmitters reaching specific receptor proteins seems logical, and it was supported for many decades. In spite of this, chemical imbalance theory fails to explain the fact that MAO inhibitors and tricyclic antidepressants have immediate effects on brain monoamine neurotransmitters; however, clinical antidepressants require several weeks of administration before they produce a therapeutic effect.

Dying cells theory explains this elapse of time between the initial treatment and the result by saying that time is needed for neurons to divide and grow. This theory is also supported by the investigations that witness such neurogenesis with experimental data. Obviously neurotransmitters do help the neurons to regenerate, but the exact mechanism for this is not known. A discovery of a solid theory on how the neurogenesis happens may lead to the development of new and hopefully better drugs that fight clinical depression.

## References

1. The World Health Organization. The World Health Report 2004: Changing History, Annex Table 3: Burden of disease in DALYs by cause, sex, and mortality stratum in WHO regions, estimates for 2002. Geneva: WHO, 2004.
2. Kessler RC, Chiu WT, Demler O, Walters EE. Prevalence, severity, and comorbidity of twelve-month DSM-IV disorders in the National Comorbidity Survey Replication (NCS-R). *Archives of General Psychiatry*, 2005 Jun;62(6):617- 27.
3. The Invisible Disease: Depression. National Institute of Mental Health. NIH Publication No. 01- 4591.  
<http://www.nimh.nih.gov/publicat/invisible.cfm>
4. NIMH Genetics Workgroup. *Genetics and mental disorders*. NIH Publication No. 98- 4268. Rockville, MD: National Institute of Mental Health, 1998.
5. Mazure CM, Bruce ML, Maciejewski PW, et al. Adverse life events and cognitive- personality characteristics in the prediction of major depression and antidepressant response. *American Journal of Psychiatry*, 2000; 157(6): 896- 903.
6. Schildkraut, J.J. (1965). "The catecholamine hypothesis of affective disorders: a review of supporting evidence". *Am J Psychiatry* 122(5): 509- 22.
7. Soares JC, Mann JJ. The functional neuroanatomy of mood disorders. *Journal of Psychiatric Research*, 1997; 31(4): 393- 432
8. Arborelius L, Owens MJ, Plotsky PM, et al. The role of corticotropin-releasing factor in depression and anxiety disorders. *Journal of Endocrinology*, 1999; 160(1): 1- 12.
9. Wilkinson, S. A recipe for violence. *Chemical and Engineering News*, 81(22):33- 37 (2003)
10. Mintun, M, Sheline, Y, Moerlein, S., et al. Decreased hippocampal 5-HT receptor binding in major depressive disorder: In vivo measurement with [<sup>18</sup>F] altanserin positron emission tomography. *Biological Psychiatry*, 2004; 55:217- 224

11. B.S. McEwen. Structural plasticity of the adult brain: how animal models help us understand brain changes in depression and systemic disorders related to depression, *Dialogues Clin Neurosci* 6 (2004), pp. 119–133
12. Richard D. Lane, Eric M. Reiman, Margaret M. Bradley, Peter J. Lang, Geoffrey L. Ahern, Richard J. Davidson and Gary E. Schwartz. Neuroanatomical correlates of pleasant and unpleasant emotion. *Neuropsychologia*, Nov. 1997; 35(11): 1437- 1444.
13. William Irwin, Michael J. Anderle, Heather C. Abercrombie, Stacey M. Schaefer, Ned H. Kalin and Richard J. Davidson. Amygdalar interhemispheric functional connectivity differs between the non-depressed. *NeuroImage*, Feb. 2004; 21(2): 674- 686.
14. Michael P. Bowley, Wayne C. Drevets, Dost Ouml;ngür and Joseph L. Price. Low glial numbers in the amygdala in major depressive disorder. *Biological Psychiatry*, Sept 2002; 52(5): 404- 412.
15. Ronald S. Duman, Shin Nakagawa and Jessica Malberg. Regulation of Adult Neurogenesis by Antidepressant Treatment. *Neuropsychopharmacology*, Dec. 2001; 25(6):836- 844.
16. Peter S. Eriksson, Ekaterina Perfilieva, Thomas Björk- Eriksson, Ann-Marie Alborn, Claes Nordborg, Daniel A. Peterson and Fred H. Gage. Neurogenesis in the adult human hippocampus. *Nature Medicine*, 1998; 4: 1313 - 1317 .
17. Paul A. Adlard, Victoria M. Perreau and Carl W. Cotman. The exercise-induced expression of BDNF within the hippocampus varies across life-span. *Neurobiology of Aging*, Apr. 2005; 26(4):511- 520.
18. Duman, D. Hippocampal neurogenesis: opposing effects of stress and antidepressant treatment. *Hippocampus*. 2006; 16(3): 239- 49
19. Duman, D. Regulation of neurogenesis and angiogenesis in depression. *Current neurovascular research*. 2004 Jul; 1(3): 261- 7
20. Farley P. 2004. The anatomy of despair. *New Scientist*, 182(2445): 42- 45.
21. Stuart Ira Fox. Human Physiology, 7<sup>th</sup> edition.