

5HTT: So is happiness all a question of length?



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What if Romeo, on learning of Juliet's death, was driven to take his life not for romantic reasons but for lack of a certain chemical substance? Enough to make Shakespeare turn in his grave! Yet a team of scientific researchers believe that melodrama may be nothing more than a question of chemistry... Indeed, a protein called 5HTT could influence our ability to deal with misfortune and certain setbacks: it would seem that people whose bodies do not produce it in a sufficient amount are more prone to depression than others.

Modern, sexist and without boundaries

Depression is a curse of our times. It is currently one of the most common psychological disorders. According to the World Health Organization, 121 million people suffer from it worldwide! And this sad record appears to be spreading with the ever-increasing stress caused by urban life. Depression occurs and sometimes recurs at all levels of society and is also sexist: women are twice as prone to it than men are. But, contrary to what is generally believed, it is universal: it is present in all parts of the world, even if people express their psychic suffering in different ways according to their cultural background. Several forms of this illness have been recorded, some more or less acute, more or less detectable, the most serious of course being that which leads to suicidal thoughts. Every year, some 10 to 20 million people attempt to commit suicide and every year, 1 million succeed. Depression, like malaria, is a killer. Which puts it 5th on the list of causes of death in the world. At

least for the time being, because by the year 2020 it will probably have reached 2nd place...

Given its frequent recurrence and although it is the psyche that is concerned, scientists have long suspected the origins of depression to be biological. Little more was needed to suggest that the culprits were genes especially when certain families are known to be more affected than others. So, while nobody dreamed of denying the importance of the environmental factor, the question still arose. However, if there was a genetic component, it remained to be proved. A team of researchers, at King's College in London, believe they have done just that. This new investigation seeks to bring "tangible" scientific data at last to a theory put forward some time ago by clinicians and epidemiologists: that is that several genes connected with psychiatric illnesses do not perhaps cause the disorder but they do influence the manner in which a person reacts to his environment.

To test a possible "genetic proneness" to depression, they chose to study a system which would logically provide a fruitful source of "candidate" genes: the serotonin system, which is precisely the target of classical antidepressants.

A depression-prone gene

In the brain, information is relayed from one nervous cell (or neuron) to another via a synapsis, which is a small space in between the cells. The neuron sending information releases a chemical substance, or neurotransmitter, into this space, which is then recognized by receptors on the surface of the receiving neuron. During this process, 10 % of the neurotransmitter molecules are wasted, whilst the remaining 90 % retained by the receptors are again released and retrieved by the neuron that initially sent them out. Serotonin is one of these neurotransmitters. More precisely, it is a "stimulating" neurotransmitter: when it links up with its receptor on the membrane of a neuron, it gives it an impulse to produce a further nervous influx towards another neuron. Serotonin is synthesized in our bodies from tryptophan, an essential amino acid; unlike other amino acids, our bodies are unable to produce it and can only obtain it from our food. Serotonin plays a part in widely differing mechanisms and controls many physiological and behavioral functions, such as sleep regulation, appetite, emotions and moods.

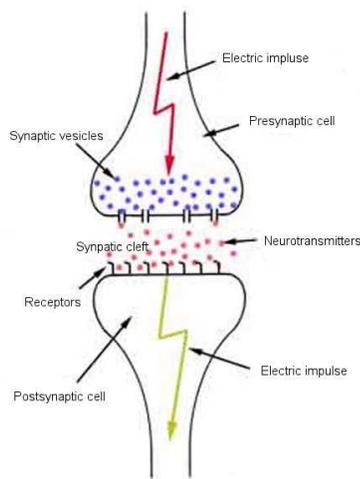


Fig.1 Synapsis

Since serotonin regulates our moods, it is involved in many psychic afflictions such as anxiety, obsessional and compulsive disorders and, of course, depression. After having noted that depressed or anxious patients often suffered from a deficiency in serotonin, researchers deduced that depression was due to a lack of

stimulation of the "receptor" neurons in the synapses known as "serotoninergetic". Since the concentration of serotonin in the synapsis depends on its retrieval by the presynaptic neurons, certain antidepressant drugs are prescribed to prevent this from happening. As a result, the serotonin remains in the synapsis longer than it normally would. This gives it a better chance to be recognized by the receptors of the postsynaptic cell, which can then be stimulated.

Why is serotonin not administered directly? Firstly because, taken orally, serotonin cannot cross the hemato-encephalic (blood-brain) barrier and so would be quite ineffective on the functions of the brain. Secondly, pure serotonin would stimulate every synapsis it encountered - even those not meant to be - whereas the antidepressants only reinforce a signal that is already present but too weak to have an effect. Thirdly, the antidepressants are selective, which means that not all synapses are involved, only those responsible for our moods and consequently depression.

This is why, in their search for genes connected with depression, the King's College researchers naturally focussed their attention on the target of these antidepressants: the "serotonin transporter or 5HTT", a protein involved in the process that allows presynaptic neurons to retrieve the serotonin released into the synapsis.

Short versus long

Every single gene - or piece of DNA - is controlled by what is known as a promoter, itself a small region of DNA situated at the beginning of the gene. The promoter controls the frequency at which the information the gene holds is used to make the corresponding protein. The promoter of the 5HTT gene exists in two forms: a long one and a short one. The long one induces a higher production of 5HTT. Moreover, it must be remembered that, with the exception of the genes which define gender, we have two copies of each gene - since at the time of fertilization we get one gene from our mother and one from our father. Hence, there are three different possibilities: we may have inherited two short versions of 5HTT, two long versions, or one short and one long. 30% of humans have two long genes, 50% one short and one long and 20% two short ones.

To try and pinpoint a possible connection between the 5HTT gene and depression, the researchers listed a number of trying, stressful situations - such as a broken love affair, bereavement, illness or loss of a job - that 847 New Zealanders aged 21 to 26 had been through. The question was, did these people suffer from depression as a consequence, and if so, what

version of the 5HTT gene did they have? 30% claimed they had felt no particular stress during that period, 25% claimed they had felt stress once, 20% twice, 11% three times and 15% four times or more. Moreover, 17% of them admitted they had gone through a major depressive period in the preceding year and 3% had tried to commit suicide, as confirmed by close friends.

The researchers' first observation was that, with regard to the number of times they had been in difficult situations, there did not seem to be a significant difference between the three genetic groups. In short, if there is a "gene of disquietude", 5HTT is not the one! In other words, people who have not lived through a stressful situation are all liable to depression whatever the length of their 5HTT gene. On the other hand, among those who have inherited two copies of the long form of 5HTT, there is always a relatively low ratio of depression however many traumatic events they have experienced. But things take a turn for the worse it seems when one or two short copies are involved: the risk of a breakdown is higher for people who have inherited one short gene, and even higher for those with two. This being so, people with two short copies and who have sustained four traumatic experiences or more are twice as liable to have a major nervous breakdown than people with two long copies and who have known as many misfortunes.

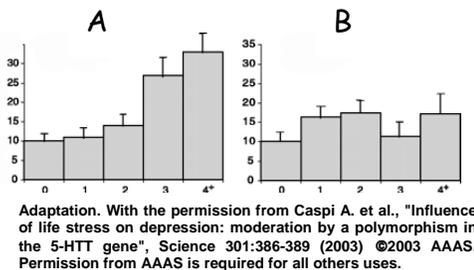


Fig.2 Diagram showing the percentage of people who fulfill the diagnostic criteria of depression at the age of 26 as a function of stressful experiences (0 to 4) between the ages of 21 and 26. For A: individuals with one or two short copies of the gene, or B: individuals with two long copies.

The 847 New Zealanders mentioned in the study belonged to the "Dunedin Multidisciplinary Health and Development Study", a research program that, from the age of 3 and for over 20 years, had submitted them to a series of tests. It was therefore possible by checking the files to establish a further link between the short version of the 5HTT gene and depression: amongst the people who had been abused as children, only those who had inherited at least one short gene

suffered from depression after the age of 18. What is more, out of the 11% who had been victims of child abuse, those who had two short copies of the gene had a 63% chance of suffering deep depression. On the other hand, for those who had two long versions, the risk stood at 30%, whether they had been abused or not in their childhood.

Custom-made antidepressants

In the same vein, a study published in 2002 attested that people with the short version of the 5HTT gene react more sharply at brain level to stimuli of fear than those with the long version. In other words, short gene owners (who produce less 5HTT) would seem to take things too seriously whereas the long gene owners are more laid back! Yet how? By what mechanism? Less 5HTT also means more serotonin in the synapses and that is what was understood to help avoid depression... For the moment, things remain relatively obscure. Moreover, the manner in which antidepressants act on 5HTT and the mechanism that attenuates depression are still not fully understood. There are also other just as effective antidepressants which conversely increase the capacity of 5HTT to retrieve serotonin, and as a result diminish its concentration in the synapses! These two totally opposed pharmacological methods question the view that, in the treatment of depression, serotonin is indeed needed to improve nervous transmission in the brain. What they do imply is that the initial effect (that is the increase or decrease of serotonin released by 5HTT) is actually only indirectly responsible for its effectiveness as an antidepressant. This all goes to show how complex the whole question is and it is recommended to regard this study with due caution.

But the day will come when 5HTT's role on our behavior will be better understood, and then it may be possible to develop treatments which will make people less vulnerable to depression. In the meantime, the discovery should enable scientists to perfect genetic tests that could identify people with a high risk for depression. But it's not for the near future because depression is most probably influenced by several genes that differ from one person to another. In fact for the moment this is what makes everyone's response to treatment unpredictable: in very rare cases, antidepressants have actually worsened symptoms of depression!

Happy pills

In documenting a hitherto elusive phenomenon, known under the interactive name of "gene-environment", this study is a first of its kind and emphasizes the importance of seeking to identify

"high risk genes" that bring on disorders, rather than the genes specific to the illness itself. In the future, this approach could extend beyond mental disorders, since there are probably genetic factors of risk for all illnesses.

The causes of depression are multiple. Prior to stress sparked off by bereavement, losing a job, failure or divorce - all "fat in the fire" - frequently lurk other problems related to childhood and education - not to mention serious issues such as incest or child abuse. All problems which constitute traumas with which we have to live and which can reappear in moments of stress in adulthood. Nowadays, Prozac is the drug prescribed but some psychiatrists regard depression as an opportunity to settle unresolved inner conflicts and therefore an opportunity for renewal. Far from being an illness, depression would be the first step towards recovery and to hinder it would check our personal development.

One could wonder whether anti-depressive treatments are indeed valid and whether taking antidepressants is a good move in the first place? But nowadays nobody has time to be ill. You have to be efficient. Antidepressants are now common and prescribed at the least sign of weakness. What's more, it takes guts to plunge into the world of psychotherapy and "trouble still waters" even with the perspective of emerging psychologically healthier. All good reasons it seems for the continuing success in the future of happy pills.

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For further information:

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- Hariri A. R. et al., "Serotonin transporter genetic variation and the Response of the human amygdala", *Science* 297:400-403(2002) PMID: 12130784

On the Internet:

- On depression (in French): <http://www.psychomedia.qc.ca/sdos2men.htm>

Illustrations:

- Fig.2, Source: AAAS, <http://www.sciencemag.org>

At UniProtKB/Swiss-Prot:

- Sodium-dependent serotonin transporter, Homo sapiens (human): P31645

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