Anxiety Biology: Is It in Your Genes?

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Biological causes refer to physiological imbalances in the body or brain that are associated with anxiety disorders. It is important to recognize that such imbalances are not necessarily the *ultimate causes* of anxiety disorders and may *themselves* be caused by

A specific hereditary vulnerability Cumulative stress over time
A hereditary vulnerability that is *brought out* by cumulative stress

Once again, it is likely that genes, life history, and stress all work together to bring about the disturbances underlying anxiety disorders.

Recent research has pointed to different types of biological explanations for different types of anxiety disorders. The type of malfunction associated with spontaneous panic attacks is probably different from the type associated with generalized anxiety disorder. And both of these, in turn, are different from physiological imbalances associated with obsessive- compulsive disorder. Each of these is discussed separately below.

I can't overemphasize that our state of knowledge about biological causes underlying anxiety disorders is still very tentative and incomplete. The brain mechanisms considered below, which are discussed after an initial section on the physiology of panic, should be viewed as hypothetical--not proven facts.

Finally, it is important to realize that even though there may be a physiological imbalance in the brain underlying your particular anxiety disorder, there is no reason to assume you can't correct it. *If you are willing to make lifestyle changes to reduce stress and upgrade your level of physical wellness, any physiological imbalances associated with panic, phobias, anxiety, or obsessions will tend to diminish and perhaps disappear altogether.* These lifestyle changes include making time for daily relaxation, an exercise program, good nutrition, social support, and self-nurturing activities (see the relevant chapters in this workbook). An alternative way to correct a biological imbalance is to rely on prescription medications that specifically alter the functioning of your brain. Medications work well in overcoming the physiological causes of anxiety disorders--though, in my opinion, they should be viewed as a last line of defense. It is often possible to correct physical imbalances *simply* by upgrading your level of health and wellness.

Later in this section you will read about mechanisms in the brain that are thought, based on recent research, to underlie panic attacks, generalized anxiety, and obsessive-compulsive disorder. First, however, is a description of the basic physiology of a panic attack--something that is much better understood.

The Physiology of Panic

What happens to your body during a panic attack? Panic is an extreme version of an alarm

reaction your body *naturally* goes through in response to any type of threat. Years ago, Walter Cannon described this as the *fight- or-flight response.* It is a built-in mechanism that enables all higher animals to mobilize a great deal of energy quickly in order to cope with predators or other immediate threats to their survival. This alarm reaction serves us well in situations that are realistically dangerous. Unfortunately, most of us also experience the fight-or-flight reaction in response to any situation that is viewed as *psychologically* dangerous, threatening, or overwhelming. An argument with your spouse or having to get up and go to work after a bad night's sleep can cause a pronounced stress response because *you perceive* it as threatening or overwhelming, even though it poses no direct risk to your survival.

In the case of a panic attack, there may be no perceived threat at all--the reaction may come on "out of the blue," without any noticeable provocation. Somehow the natural fight-or-flight response has gotten out of control. That it occurs out of context and without apparent reason suggests that the brain mechanisms that control the response aren't functioning properly. The current hypothesis about the nature of this dysfunction is described in the next section. The physiology of panic itself, however, is better known.

Your nervous system has two separate actions: *voluntary* and *involuntary*. There is a voluntary nervous system that moves your muscles and obeys your direct command. Your involuntary nervous system, on the other hand, regulates automatic functions ordinarily outside voluntary control, such as your heartbeat, respiration, and digestion. This involuntary system is itself divided into two branches: the *sympathetic* and *parasympathetic* nervous systems. The sympathetic nervous system is responsible for mobilizing a number of reactions throughout your body whenever you're emotional or excited. The parasympathetic nervous system has an opposite function. It maintains normal, smooth functioning of your various internal organs during times when you are calm and at rest.

In a panic attack, your sympathetic nervous system sets off several different bodily reactions rapidly and intensely. First, it causes your adrenal glands to release large amounts of adrenaline. What you feel is a sudden "jolt," often accompanied by a feeling of dread or terror. Within seconds, the excess adrenaline can cause 1) your heart to race, 2) your respiration to become rapid and shallow, 3) profuse sweating, 4) trembling and shaking, and 5) cold hands and feet. Your sympathetic nervous system also produces muscle contractions (the most extreme case of this is when animals "freeze" in fear), possibly leading you to experience strong contractions in your chest or throat along with a fear of not being able to breathe. Other reactions caused by the sympathetic nervous system include excess release of stomach acid, inhibition of digestion, release of red blood cells by the spleen, release of stored-up sugar by the liver, an increase in metabolic rate, and dilation of the pupils.

All of these reactions occur to a lesser degree when you are emotional or excited. The problem in

panic is that they peak to such an extreme level that you feel overwhelmed, feel terrified, and have a strong urge to run. It is important to realize that the adrenaline released during panic tends to be reabsorbed by the liver and kidneys within a few minutes. If you can "ride out" the bodily symptoms of panic without fighting them or telling yourself how horrible they are, they will tend to subside within a short time. Chapter 6 will describe strategies for learning to observe rather than react to the bodily symptoms of panic. By breathing properly and making supportive, calming statements to yourself, you can learn to manage panic instead of scaring yourself into a much more intense reaction.

While the physiology of panic is well understood, the mechanisms in the brain that initiate these physiological reactions are less well understood. The following section presents a recent hypothesis about a particular imbalance in the brain thought to be responsible for panic attacks.

Panic Attacks

Your brain is by far the most complex system in your body, consisting of over one hundred billion brain cells or neurons. At any given moment in time, millions of nerve impulses are being transmitted along multiple pathways which interconnect various regions of your brain. Every time a single nerve impulse moves from one nerve cell to the next, it must cross a space. Individual nerve cells are not connected but are separated by tiny spaces called *synapses*. It has been known for some time that the process by which a nerve impulse moves across a synapse is chemical in nature. Microscopic amounts of chemicals secreted into the synapse allow transmission of a nerve impulse from one neuron to the next. These chemicals are called *neurotransmitters*; there are over twenty different types of them in the brain.

It appears that there are different systems in the brain that are especially sensitive to particular neurotransmitters. Each system consists of a vast network of nerve cells *(neurons*) that are sensitive to a particular neurotransmitter. One system, called the *noradrenergic system*, seems to be especially sensitive to a neurotransmitter substance called *norepinephrine*. Another system, the *serotonergic* system, contains neurons especially sensitive to a neurotransmitter substance called *serotonin*. Both systems have a large number of receptor sites (sites on nerve cells that respond to neurotransmitters) in some of the major structures of the brain that are activated during a panic attack. Specifically, the *amygdala*--a structure in your brain--is thought to play a key role in instigating panic. Research has found that the amygdala does not act alone but works in concert with a variety of other structures that all contribute to stimulating panic. These structures include "higher" brain centers such as the prefrontal cortex and insula, which serve to modulate sensory information, interpreting it as "dangerous" or "safe." Such information is stored in memory in a part of the brain called the *hippocampus*. The higher brain centers and the hippocampus interface directly with the amygdala. The amygdala, in turn, instigates panic by stimulating a variety of other brain structures, including

1) the *locus coeruleus*, which contributes to general behavioral and physiological arousal, 2) the *hypothalamus*, which regulates the release of adrenaline (via the pituitary gland, stimulating your adrenal glands) and also stimulates your sympathetic nervous system (see the previous section),

the *periaqueductal gray region*, which stimulates defensive and avoidance behavior, and, finally, 4) the *parabrachial nucleus*, which stimulates increased respiration.

Within your brain, panic attacks are more likely to occur when this entire system is *overly sensitized*, perhaps from having been previously activated too frequently, too intensely, or both. Thus the neurological basis for panic is not exactly a "chemical imbalance," as your doctor may have told you, but an overly sensitized "fear system," including all of the above brain structures. Researchers believe that deficiencies of the neurotransmitters serotonin and norepinephrine may contribute to *insufficient inhibition* of the amygdala, locus coeruleus, and associated structures that make up this fear system. That is why SSRI (selective serotonin reuptake inhibitors) or tricyclic antidepressant medications, which increase the amounts of serotonin and norepinepherine available throughout your brain, can diminish panic attacks. Over a period of two to four weeks, these?medications seem to be able to *stabilize* and *desensitize* an overly sensitized amygdala, locus coeruleus, and associated fear system.

What *causes* the original over sensitization of the fear system remains unclear at this time. One hypothesis is that changes in this system can take place as a result of acute stress or as the long-term result of multiple stressors over time. Although this hypothesis remains unproven, it seems likely that *cumulative stress contributes in an important way to the onset of panic attacks* (as discussed earlier in this chapter). If this hypothesis about stress altering the amygdala and the fear system turns out to be true, an important implication follows: *the most effective long-term treatment for brain dysfunctions associated with panic disorder is a consistent and comprehensive program for reducing stress in your life*. Medications can? certainly help restabilize structures in your brain that contribute to panic and anxiety in the short run. Yet without changes in your lifestyle (such as? regular relaxation and exercise, good time management, proper nutrition, personal support, and constructive attitudes)--changes that allow you to live more simply and peacefully--panic and anxiety will tend to return after the medications are withdrawn.

Generalized Anxiety

Benzodiazepine tranquilizers, such as Xanax, Ativan, or Klonopin, can very effectively reduce generalized anxiety (as well as anticipatory anxiety in panic and phobic disorders). It has been discovered that a specific system in the brain, the GABA system, is uniquely sensitive to benzodiazepine drugs. This system consists of neurons that are sensitive to the neurotransmitter gamma-aminobutyric acid (GABA for short). GABA functions naturally in the brain as an inhibitory neurotransmitter--it tends to inhibit, or "tone down," brain activity, particularly in the limbic system,

which is the brain's center for emotions. Thus GABA is associated with the brain's own natural calming response. When you give people GABA directly, or give them drugs that increase the activity of the GABA system, their anxiety decreases.

It appears that benzodiazepine tranquilizers like Xanax stimulate the GABA system to be more active, just as the neurotransmitter GABA itself does. That is why these tranquilizers tone down anxiety, as well as any other form of emotional arousal.

What is going on with the GABA system in persons who are chronically anxious? Several hypotheses have been proposed. There may be a deficiency of GABA itself, resulting in less inhibitory activity of the GABA system. Or there may be a deficiency of some naturally occurring benzodiazepine substance in the brain (yet to be identified) which leads to reduced activity of the GABA system. Perhaps there are too many GABA receptors relative to the amount of GABA available. The situation is quite complicated because brain activation (hence anxiety) is controlled not only by the GABA system but by the serotonin and norepinephrine systems (and even other neurotransmitter systems) as well. Moreover, brain research has found that these systems all interact and modulate each other. Suffice it to say that the GABA system plays a major role in the neurobiological basis of generalized anxiety. Deficient activation of the GABA system results in insufficient inhibition of limbic system structures, such as the amygdala and locus coeruleus, which contributes to all forms of anxiety.

Obsessive-Compulsive Disorder

The same reasoning that applied to generalized anxiety disorder also applies to obsessive-compulsive disorder (OCD). The effectiveness of specific drugs, such as clomipramine (Anafranil) and SSRI antidepressants (selective serotonin reuptake inhibitors)--fluoxetine (Prozac), sertraline (Zoloft), paroxetine (Paxil), and fluvoxamine (Luvox)--in reducing obsessive-compulsive symptoms tells us something about the possible biological mechanisms for obsessive-compulsive disorder. These drugs are known to increase the amount of a specific neurotransmitter substance, serotonin, in the brain. They do so more effectively than most other antidepressant medications. So we know that serotonin (and the serotonin system of the brain) plays an important role in the neurobiological basis of OCD.

Recent brain research has identified an OCD "neurocircuit" in the brain involving three brain structures: the *orbitofrontal cortex, thalamus,* and *caudate nucleus.* These structures define a circuit, or "loop," that brain imaging studies have found to be overly active in persons with OCD. When you worry, the orbitofrontal cortex sends a worry signal to the thalamus, which in turn sends the signal back (via the caudate) to the orbitofrontal cortex for interpretation. In normal people, this cycle happens only once or a few times. In people with OCD, however, because of a problem in the caudate nucleus, the signal goes back and forth and "loops" many, many times. It appears that

SSRIs work by toning down excess activity of this OCD circuit. Many serotonin neurons in the brain are inhibitory in function, and there appears to be an abundance of these inhibitory neurons in the structures that make up the OCD loop. Thus increasing serotonin in the brain increases the activity of the inhibitory serotonin neurons, which in turn "brakes" excess activity in the OCD circuit.

Another brain structure involved in OCD is the *anterior cingulate gyrus*. One function of the cingulate is to enable you to flexibly shift attention from one topic to another. When the cingulate isn't functioning properly, you can more easily get "stuck" or get locked into a particular theme, as is the case when you are obsessing on something. It appears that SSRI medications help the cingulate to function better. Brain imaging research has also found that cognitive behavioral therapy, specifically exposure and response prevention, can normalize brain function in the structures associated with OCD. It's quite exciting to see that a strictly psychological intervention can result in lasting changes in brain function similar to what drugs can accomplish.

Medical Conditions That Can Cause Panic Attacks or Anxiety

The physiology of panic described at the beginning of this section is well established. But the various proposed explanations of the biological mechanisms involving different neurotransmitter systems of the brain are, at present, still hypothetical. It is important to keep in mind that these biological hypotheses apply to a majority *but not all cases* of panic attacks and generalized anxiety. Sometimes panic reactions or anxiety can arise from medical conditions that are quite separate from recognized anxiety disorders. Hyperthyroidism and hypoglycemia, for example, can cause panic attacks that are by all appearances identical to those seen in panic disorder. A calcium or magnesium deficiency or an allergy to certain food additives can also produce panic or anxiety. When these conditions are corrected, the anxiety disappears.

Any of the following conditions might be a cause of panic attacks or generalized anxiety. The first six are the ones most frequently seen.

Hyperventilation Syndrome

Rapid, shallow breathing at the level of your chest can sometimes lead to excessive lowering of carbon dioxide in your bloodstream. This results in symptoms very similar to those of a panic attack, including light-headedness, dizziness, feelings of unreality, shortness of breath, trembling, and/or tingling in your hands, feet, or lips. These symptoms, in turn, may be perceived as dangerous and may stimulate a bona fide panic attack. (See the section on abdominal breathing in chapter 4 for further discussion of hyperventilation.)

Hypoglycemia

For a large number of people, blood sugar levels can fall too low as a result of improper diet or

simply stress. When this happens, such people experience a variety of symptoms similar to a panic reaction, including anxiety, shakiness, dizziness, weakness, and disorientation. Hypoglycemia can cause panic attacks, or, more often, can aggravate panic reactions that are caused by other factors. (See chapter 15 for a detailed discussion.)

Hyperthyroidism

Excessive secretion of thyroid hormone can lead to heart palpitations (rapid heartbeat), sweating, and generalized anxiety. Other symptoms of hyperthyroidism include weight loss, elevated body temperature, insomnia, and bulging eyes. If you have several of the above symptoms, you might want to have your doctor do a thyroid panel to see if this condition is contributing to your anxiety or panic symptoms.

Mitral Valve Prolapse

Mitral valve prolapse is a harmless condition that causes heart palpitations. It is caused by a slight defect in the valve separating the upper and lower chambers on the left side of your heart. Blood moves through the mitral valve as it passes from the upper to the lower chamber. With mitral valve prolapse, the valve doesn't close completely and some of the blood can flow back from the lower to upper chamber, causing the heart to beat out of rhythm. The resulting rhythm disturbance can be disconcerting enough to cause some people to panic--but it is *not* dangerous. Mitral valve prolapse is *not* a cause of heart attacks.

For reasons that are unclear, mitral valve prolapse occurs more frequently in people with panic disorder than in the population at large. In severe cases, it can be treated through the use of beta-blocking drugs such as Inderal.

Premenstrual Syndrome (PMS)

If you are a woman, it is important to observe whether your panic reactions (or generalized anxiety) worsen around the time just before your period. If so, treating your PMS may be enough to alleviate your problem with panic or anxiety. Treatment usually involves improvements in diet and exercise, taking supplements such as vitamin B6, and in some cases taking natural progesterone. (See chapter 16 for a more detailed discussion.)

Inner Ear Disturbances

For a small proportion of the population, panic attacks seem to be associated with a disturbance in balance caused by swelling of the inner ear (due to infection, allergy, Ménière's syndrome, or other problems). If

dizziness, light-headedness, and/or unsteadiness are a *prominent* part of your problem with

anxiety or panic, you may want to consult an otolaryngologist to check the labyrinth system of your inner ear.

Other medical conditions that can cause panic or anxiety include the following:

Acute reaction to cocaine, amphetamines, caffeine, aspartame, appetite suppressants, asthma medications, steroids, or other stimulants
Withdrawal from alcohol, sedatives, or tranquilizers Thyrotoxicosis
Cushing's syndrome Adrenal tumor Parathyroid disease
Partial complex seizures (temporal lobe epilepsy) Post-concussion syndrome
Deficiencies of calcium, magnesium, potassium, niacin, vitamin B12
Emphysema Pulmonary embolism Cardiac arrhythmias
Congestive heart failure Essential hypertension
Environmental toxins such as mercury, carbon dioxide, hydrocarbons, food additives, pesticides

To adequately rule out any medical conditions that could be causing or aggravating your particular problem, have your doctor give you a thorough physical examination, including a blood panel, before adopting behavioral and psychological strategies for recovery. Keep in mind, though, that the above medical conditions (with the exception of hyperventilation and hypoglycemia) contribute to panic or anxiety in only a minority of cases.