Is There a Gene for Postpartum Depression?

The transition to parenthood is filled to the brim with behavioral extremes. Parents who are otherwise emotionally stable are in one moment thrilled and happier than they have ever been and confused and fearful the next. A friend of mine once theorized that these reactions occur because “parenting is an amateur sport” played by persons who are highly motivated to do the right thing but who often have no idea what that right thing is.

For some couples, the transition to parenthood is not filled with this rich mixture of great perplexity and great joy. For them, parenthood is mostly filled with sadness and even despair. Postpartum depression was originally coined to describe this experience in the mother, although it is becoming clear that fathers can experience very similar emotions too.

Is there a molecular basis for postpartum depression—at least for the type that mothers experience? Recent findings, which I describe here, may answer this question. First, we will focus on several background behavioral and molecular issues and then move on to some interesting data about births in genetically manipulated laboratory animals. Feel free to skip to the “Data” section if postpartum depression rates and γ-aminobutyric acid (GABA) receptor biology are working parts of your vocabulary. As you know, the probability of experiencing major depression is twice as high in women as it is in men, and pregnancy does not buffer against this risk. Postpartum depression afflicts about 20% of mothers. Higher rates are seen in adolescent mothers than in older mothers.

Mental health professionals who are considering treatment for a depressed pregnant patient must make choices that can be particularly troublesome. Many clinicians are concerned about the potentially damaging effects of antidepressant medications on the developing fetus. Should a woman be treated during pregnancy? As I have discussed in this space before, serotonin plays a dramatic role in gestational brain development, especially in the thalamus. Concerns about serotonin’s effects on brain development actually held up the FDA’s approval of fluoxetine.

This risk is also observable after parturition. If depression remains untreated, the risk of drug and alcohol abuse and suicide and infanticide greatly increases. Yet, psychotropic drugs may expose a breast-fed baby to these medications. Are there risks associated with this exposure? The possibility of adverse consequences is not zero, although there is a critical need for further research in this area. As if pregnancy were not complicated enough, balancing the risk of potential behavioral consequences of depression with the pharmacological risk of treatment is quite challenging indeed.

There is increasing evidence that men can also experience depression after the birth of their child. The rates can be astonishingly high—about 1 in 4 fathers are affected in some studies; this rate climbs to 1 in 2 if his spouse is also depressed. The effect can be recursive. Loss of emotional support from the female because of depression may cause or exacerbate depression in the male, which in turn may retrigger depressive behaviors in the female.

Depression is a big deal for some families in the transition to parenthood; it is thus gratifying to report some very promising findings regarding its molecular underpinnings. We need only one more piece of background information, which involves a very particular animal model of depression, to understand it fully.

Molecular background issues

The literature that reviews the molecular processes in human depression often focuses on the seminal roles of catecholamines and indoleamines. Over the years, it has become increasingly clear that other neurotransmitter systems can also mediate the pathogenesis of depression, notably glutamate and GABA. One of GABA’s attendant receptors plays a prominent role in our story.

Often contrasted with glutamate (the canonical excitatory neurotransmitter), GABA is characterized as the brain’s classic “inhibitory” neurotransmitter. Glutamate and GABA function together as a kind of molecular yin-yang by regulating neuronal activity throughout the CNS. GABA mediates its effects by binding to 1 of 3 transmembrane receptors in specific neurons in the brain (awkwardly called “GABAergic” cells). The binding results in the opening of ion channels, creating a localized increase in the negativity across the plasma membrane. This hyperpolarization of the cell (as opposed to depolarization, which results in a more equal distribution of charge across the membrane) produces the inhibitory effect.

GABA is not always inhibitory. Most of its electrical effects depend on localized current flow in adult cells and even the stage of the development of the cell. In neonatal tissues, GABA acts as an excitatory neurotransmitter and makes a change in its job description only as the tissues mature.

As noted, GABA exerts its effects by binding to 1 of 3 members of the GABA receptor family: GABA_A, GABA_B, and GABA_C. GABA_A and GABA_C are ionotropic receptors. As their name implies, these receptors function directly as the ion channels. GABA_B opens ion channels in a less direct fashion. A classic metabotropic receptor, GABA_A is a protein-coupled and participates in a signal transduction process that eventually results in the opening of other ion channels. These proteins are complex structures that are composed of smaller subunit proteins (the GABA_A receptor has one called the “γ subunit,” which will be important to our story).

Before we get started on the data, it might be useful to go over one last critical issue. Over the years, a number of animal models have been used to increase our understanding of the molecular substrates undergirding developmental processes. Although there have been a fair number of animal models that mimic aspects of human anxiety disorders, relatively few can be reliably used in the study of human depression.

One of the animal tests that is used often involves creating standardized depressive behavior in mice using the Porsolt forced swim test. Another test involves measuring anhedonia, in which the ability to experience pleasure from normally pleasurable activities is inhibited. Both were deployed in the data that I will describe next.

The data

The researchers decided to focus on the GABA_A receptor for an important reason: the GABA_A receptor is one of the principal targets for the action of many neuroactive products of steroid hormones that are usually called “neurosteroids.”

Altered neurosteroid levels have been associated with a wide variety of psychiatric illnesses, including premenstrual syndrome and postpartum depression. A large increase in levels of progesterone-derived neurosteroids occurs during pregnancy, then levels decline rapidly after birth. Understanding how these levels interact with the GABA_A receptor biology turned out to be an important area of inquiry.

The researchers noticed that GABA_A receptor expression was greatly attenuated in the hippocampus of female mice during pregnancy. The loss of the receptor mediated a change in the electrical properties of the tissue, which was demonstrated by whole-cell, patch-clamp recordings (patch-clamp involves using electrodes to record currents in single neurons). Researchers also noticed that this effect was reversed in the postpartum period. The levels of the GABA_A receptor rapidly returned to baseline after the females had given birth.

Knocking out the GABA_A

How would an animal behave if it did not have this receptor or at least one of its subunits? If baseline levels could not ever return in these animals, would they exhibit depressive-like symptoms?

One way to answer this question would be to create knock-out mice that are raised without GABA_A. Knock-out mice are genetically engineered to develop without a particular genetic sequence. They present the researcher with a site-specific loss of function. Hints as to the functioning of the knock-out gene sequence can be obtained simply by noting abnormalities in the function or behavior of the animal (Figure).

It is a risky procedure. Some genes are so critical to gestational progress that their disruption results in the death of the animal, often in utero.
The researchers knocked out only the γ subunit we discussed previously. Without this subunit, receptor function is crippled. Happily, the animals survived.

The researchers were able to show depressive symptoms in the knockout mice after birth. After the administration of the standardized Porst and anhedonia tests mentioned previously, the animals exhibited robust depressive characteristics. There was a disturbingly large increase in the overall pup mortality in this population. The manipulated mothers were much more likely to neglect or cannibalize their pups compared with unmanipulated littermate controls.

The last series of experiments involved the use of 4,5,6,7-tetrahydroisoxazolo(5,4-c)pyridin-3-ol (merci-fully shortened to THIP, also called “gaboxadol”). This drug, which was first characterized as a sedative, has an extraordinary property: it is a specific GABA receptor agonist. THIP can fully restore receptor function, even in an animal that has lost its utility because of a subunit knock-out.

When these animals were treated with THIP, the depressive behaviors measured by the standardized tests and maternal behavior toward the pups vanished, and normal behavior was observed. The presence of functioning GABA receptors appeared to be the independent variable in these experiments. Keep them present and normal behavior was observed. Reduce their levels (and inhibit their ability to reestablish themselves) and depression returns. You can turn it on and off like a light switch.

Conclusions
Could these data be used to explain postpartum depression? They certainly suggest compelling new lines of research. Remember that it is normal for elevated levels of progesterone-derived neurosteroids to down-regulate GABA receptor concentrations during pregnancy and then to reestablish themselves after birth. Could postpartum depression in women be understood as an inability for these receptors to bounce back after birth? If so, it might be possible to test for such a lack of restoration with noninvasive imaging technologies. Is it possible that mutations in the receptor or in molecular moieties, which regulate receptor number, prevent their reestablishment to prepregnancy levels? Could these mutations predict depressive experiences? If so, the isolation of the first gene for postpartum depression might actually be in hand. Using THIP or its derivatives as a possible treatment, there may even be some hope for pharmacological intervention. Promising data indeed, but only promising.

My usual objections about applying animal research to human behavior hold here, certainly. The mouse cortex is, after all, about the size of a postage stamp, while the human cortex is about the size of a baby blanket. Compelling as these data are, they only suggest areas for human research directions.

These data do not solve the most common nature/nurture issues that dog most behavioral research like this, of course. It is especially important for affective disorders. Data suggest that the relative risk for depression is two-thirds environmental and one-third genetic. Because fathers can also experience depression, which can profoundly influence the spouse, that also must be factored in and perhaps saddled with more weight than other environmental influences.

None of these objections are deal killers. These data may point to the presence of a chromosomal abnormality as a risk factor for depression. It would then suggest that unusually close attention should be paid to any mother who has the chromosomal risk factor. These data may ultimately explain why the transition to parenthood (amateur sport that it is), although never easy for anyone, can be so catastrophically overwhelming to some.

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**Figure**

A gene for postpartum depression?

Shown below are experiments that may link expression of the receptor with depressive symptoms—at least in mice. The first panel shows unmanipulated control animals. The second panel shows animals whose GABA receptor has been “knocked-out” (see text). The third panel shows the same knock-out animals; however, they have now been treated with the GABA receptor-subunit agonist, 4,5,6,7-tetrahydroisoxazolo(5,4-c)pyridin-3-ol (THIP).