Serotonin, Motor Activity and Depression-Related Disorders

Clues to the origin and treatment of depression and obsessive-compulsive disorders can be found in the role of serotonin neurons in the brain

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Prozac, Zoloft and Paxil are drugs that have been widely celebrated for their effectiveness in the treatment of depression and obsessive-compulsive disorders. The popular press has also made much of Prozac's ability to alleviate minor personality disorders such as shyness or lack of popularity. The glamorous success of these drugs has even inspired some writers to propose that we are at the threshold of a new era reminiscent of Aldous Huxley's Brave New World, in which one's day-to-day emotions can be fine-tuned by simply taking a pill. Yet for all the public attention that has been focused on the apparent benefits of Prozac-like drugs, the fundamental players in this story—the cells and the chemicals in the brain modified by these drugs—have been largely ignored.

This is partly a consequence of the complexity of the nervous system and the fact that so little is known about how the activity of cells in the brain translates into mood or behavior. We do know that Prozac-like drugs work by altering the function of neurons that release the signaling chemical (neurotransmitter) serotonin. Serotonin has been implicated in a broad range of behavioral disorders involving the sleep cycle, eating, the sex drive and mood. Prozac-like drugs prevent a neuron from taking serotonin back into the cell. Hence Prozac and related drugs are collectively known as selective serotonin reuptake inhibitors, or SSRIs. In principle, blocking the reuptake of serotonin should result in a higher level of activity in any part of the nervous system that uses serotonin as a chemical signal between cells. The long-term effects of these drugs on the function of a serotonin-based network of neurons, however, are simply not known.

My colleagues and I have attempted to understand the role of serotonin in animal physiology and behavior by looking at the activity of the serotonin neurons themselves. For more than 10 years at Princeton University, Casimir Fornal and I have been studying the factors that control the activity of serotonin neurons in the brain. I believe these studies provide the linchpin for understanding depression and obsessive-compulsive disorders and their treatment with therapeutic drugs. Our work provides some unique and unexpected perspectives on these illnesses and will serve, we hope, to open new avenues of clinical research.

Serotonin, Drugs and Depression

Communication between neurons is mediated by the release of small packets of chemicals into the tiny gap, the synapse, that separates one neuron from another. The brain uses a surprisingly large number of these chemical neurotransmitters, perhaps as many as 100. However, the preponderance of the work is done by four chemicals that act in a simple and rapid manner: glutamate and aspartate (both of which excite neurons) and gamma-aminobutyric acid (GABA) and glycine (both of which inhibit neurons). Other neurotransmitters, such as serotonin, norepinephrine and dopamine are somewhat different. They can produce excitation or inhibition, often act over a longer time scale, and tend to work in concert with one of the four chemical workhorses in the brain. Hence they are also referred to as neuromodulators.

Even though serotonin, norepinephrine and dopamine may be considered to be comparatively minor players in the overall function of the brain, they appear to be major culprits in some of the most common brain disorders: schizophrenia, depression and Parkinson's disease. It is interesting to observe that glutamate, aspartate, GABA and glycine are generally not centrally involved in psychiatric or neurological illnesses. It may be the case that a primary dysfunction of these systems is incompatible with sustaining life.

Serotonin's chemical name is 5-hydroxytryptamine, which derives from the fact that it is synthesized from the amino acid L-tryptophan. After a meal, foods are broken down into their con-

Figure 1. Frontispiece of Robert Burton's 17th-century classic, The Anatomy of Melancholy, depicts various icons linking depression and slowness of movement. Foremost among these are the human figures presented in pensive and withdrawn poses, and the astronomical symbol for Saturn (stylized "h", top, center), representing lethargy and gloom. In Burton's century, scientific views of depressive illnesses had not developed beyond those of ancient Greece, in which human personality was thought to be the result of four humors, or fluids, in the body. In this view, depressed persons (and scholars) were thought to have an excess of black bile, and hence were "melan-cholic." Here the Greek philosopher Democritus (top, center) is depicted with the remains of various animals that had been annotated to find the source of the black bile. In contrast to the ancients' view that melancholy resulted from an excess of black bile, contemporary views hold that low levels of the neurotransmitter serotonin may account for many of the symptoms associated with depressive illnesses. The author proposes that serotonin may also be the link between low levels of motor activity and depressed moods. (Photograph Courtesy of Duke University Special Collections)
THE ANATOMY OF MELANCHOLY.

What it is with all the kind causes, symptoms, prognosticks, & severall cures of it.

In three Partitions, with their severall Sections, members & subjections.

Philosophically, Medicinally, Historically, opened & cut vp.

By

Democritus Junior.

With a Satyrical Preface, conducing to the following Discourses.

The fourth Edition, corrected and augmented by the Author

Omne tulit punctum, qui mouet while rules.

Oxford
Printed for Henry Cripps
The obvious benefit of the selective serotonin reuptake inhibitors is that their action is effectively limited to the reuptake of serotonin. This probably accounts for the fewer side-effects experienced by people taking SSRIs. Like other antidepressant drugs, the SSRIs have a therapeutic lag. They typically require 4 to 6 weeks to exert their full effects. Claude DeMontigny and his colleagues at McGill University have suggested that one of the consequences of increasing the levels of serotonin in the brain is a compensatory feedback inhibition that decreases the discharge of brain serotonergic neurons. This results in a "zero sum game" in which there is no net increase in functional serotonin. However, with continuous exposure to serotonin, the receptors mediating this feedback inhibition (the 5-HT₁A receptor) become desensitized. It is hypothesized that after several weeks this results in progressively less feedback, increased serotonergic neurotransmission and clinical improvement.

Behavior of Serotonin Neurons
Essentially all of the serotonin-based activity in the brain arises from neurons that are located within cell clusters known as the raphe nuclei. These clusters of serotonin neurons are located in the brainstem, the most primitive part of the brain. It is not surprising, then, that serotonin appears to be involved in some fundamental aspects of physiology and behavior, ranging from the control of body temperature, cardiovascular activity and respiration to involvement in such behaviors as aggression, eating and sleeping.

The broad range of physiology and behavior associated with serotonin’s actions is at least partly attributable to the widespread distribution of serotonin-containing nerve-fiber terminals that arise from the raphe nuclei. Indeed, the branching of the serotonin network comprises the most expansive neurochemical system in the brain. Serotonin neurons project fibers to virtually all parts of the central nervous system, from the various layers of the cerebral cortex down to the tip of the spinal cord.

Since the raphe nuclei contain only a few hundred thousand neurons, and the brains of large mammals (cats, monkeys and people, for example) contain hundreds of billions of neurons, the serotonin neurons constitute less than one-millionth of the total population of neurons in the brain. Despite being so

stilbene amino acids, including tryptophan, and then transported throughout the body by the circulatory system. Once tryptophan is carried into the brain and into certain neurons, it is converted into serotonin by two enzymatic steps.

Serotonin’s actions in the synapse are terminated primarily by its being taken back into the neuron that released it. From that point, it is either recycled for reuse as a neurotransmitter or broken down into its metabolic by-products and transported out of the brain. With this basic understanding of serotonin neurotransmission, we can begin to understand the mechanisms of action of antidepressant drugs.

One of the earliest antidepressant drugs, iproniazid, elevates the level of a number of brain chemicals by inhibiting the action of an enzyme, monoamine oxidase, involved in their catabolism. For example, monoamine oxidase inhibitors (MAOIs) block the catabolism of serotonin into its metabolite, 5-hydroxyindole acetic acid (5-HIAA), leading to a buildup of serotonin in the brain. Unfortunately, because monoamine oxidase catalyzes a number of brain chemicals (including norepinephrine and dopamine), there are a number of side-effects associated with these drugs. Some interactive toxicity of MAOIs is also a major drawback for their use in the treatment of depression.

Tricyclic antidepressants (so named because of their three-ringed chemical structure), do not share the interactive toxicity of MAOIs. Tricyclics such as imipramine act to block the reuptake of serotonin from the synapse back into the neuron that released it. In a sense, this floods the synapse with serotonin. These drugs are quite effective in treating depression, but they also induce some unpleasant side-effects, such as constipation, headache and dry mouth. This may be due to the fact that tricyclic antidepressants not only block the reuptake of serotonin, but also exert similar effects on norepinephrine and dopamine.

Figure 2. Clusters of serotonin neurons located in the raphe nuclei (colored areas) within the brainstem project throughout most regions of the forebrain, brainstem, cerebellum and spinal cord. The widespread distribution of the serotonin-releasing fibers at least partially accounts for the system’s influence over such basic functions as the sleep cycle, the sex drive, eating, body temperature, cardiovascular activity, respiration, mood and aggression. (Adapted from the work of Efrain Azmitia, New York University.)
vastly outnumbered, serotonin neurons have immense importance: Each one exerts an influence over as many as 500,000 target neurons. In this light the activity of individual serotonin neurons bears a closer look.

The behavior of any neuron is typically measured by its electrical activity. One of the more remarkable electrical phenomena is a cell-wide discharge called an action potential, or spike. Action potentials result from the movement of charged particles (potassium and sodium ions) into and out of the cell through specialized channels in the membrane. Action potentials are an important aspect of a neuron's behavior because the rate and pattern of their occurrence is thought to encode information that is conveyed to other cells. They are central to our story because, in the case of serotonin neurons, each electrical discharge results in the release of a small packet of serotonin from the cell, which in turn alters the activity of target cells bearing serotonin receptors. (At this writing, at least 14 types of serotonin receptors are known, each of which contributes to the diverse effects of serotonin throughout the brain.)

Serotonin neurons have a characteristic discharge pattern that distinguishes them from most other cells in the brain. They are relatively regular, exhibiting a slow and steady generation of spikes. Serotonin neurons retain this rhythmic pattern even if they are removed from the brain and isolated in a dish, suggesting that their clocklike regularity is intrinsic to the individual neurons.

One of the first significant discoveries about the behavior of serotonin neurons in the brain was that the rate of these discharges was dramatically altered during different levels of behavioral arousal. When an animal is quiet but awake, the typical serotonin neuron discharges at about 3 spikes per second. As the animal becomes drowsy and enters a phase known as slow-wave sleep, the number of spikes gradually declines. During rapid-eye movement (REM) sleep, which is associated with dreaming in human beings, the serotonin neurons fall completely silent. In anticipation of waking, however, the neuronal activity returns to its basal level of 3 spikes per second. When an animal is aroused or in an active waking state, the discharge rate may increase to 4 or 5 spikes per second.

Since early experimental studies had linked serotonin to so many behavioral and physiological processes, one of our first priorities was to examine the activity of serotonin neurons in animals exposed to a wide variety of conditions. We chose to perform these studies on cats since their brains and their raphe nuclei have been described in considerable detail. While we recorded the electrical activity of individual serotonin neurons in the brain, we exposed cats to various stressors such as loud noise, physical restraint, a natural enemy (a dog), a heated environment, a fever-inducing agent, drug-induced changes in blood pressure, and insulin-induced changes in plasma glucose lev-

Figure 3. Activity at the site of a serotonin synapse between two neurons involves both the release and reuptake of the neurotransmitter. Serotonin (black) is synthesized from the amino acid tryptophan and sequestered within small packets or vesicles. The arrival of an action potential at the presynaptic terminal results in the release of serotonin from the vesicles into the synaptic gap. The binding of serotonin to specialized receptors on the postsynaptic neuron produces a reaction that alters the electrical and chemical activity of the receiving neuron. Serotonin is removed from the synaptic cleft by another mechanism that takes the neurotransmitter back into the presynaptic terminal, where it is reused or degraded into its primary metabolite, 5-hydroxyindole acetic acid (5-HIAA). Antidepressant drugs such as iproniazid inhibit the enzyme monoamine oxidase (MAO), which normally acts to degrade serotonin. A new generation of antidepressant drugs, including selective serotonin reuptake inhibitors such as Prozac, allow serotonin to remain in the synaptic cleft by blocking its reuptake into the presynaptic neuron. Consequently, the functional activity of serotonin is increased.

Figure 4. Serotonin neurons in the raphe nuclei number only a few hundred thousand and yet exert enormous influence in the brain. Each serotonin neuron makes connections with at least 500,000 other neurons. Here the appearance of a few serotonin neurons is revealed with an antibody to the 5-HT1A autoreceptor, which is distributed on the surfaces of the neurons. (Courtesy of Efraim Azmitia, New York University.)
Figure 5. Activity of a serotonin neuron varies across an animal's sleep-wake-arousal cycle. The neuron's clocklike generation of action potentials ranges from 5 per second in the active waking state to about 0 per second during rapid-eye-movement (REM) sleep. The absence of muscle tone during normal REM sleep (when serotonin neurons are inactive) suggests a possible link between the activity of serotonin neurons and the facilitation of muscle activity.

els. These conditions would be stressful to any animal and, not surprisingly, each of these stressors resulted in dramatic changes in the animal's behavior and activated its emergency defenses, including certain parts of its autonomic nervous system. Remarkably, however, none of these conditions significantly changed the activity of the serotonin neurons beyond that seen during a spontaneous active state. The results were perplexing. If these powerful stimuli could not perturb a serotonin neuron, what would?

The variable activity of serotonin neurons during different stages of the sleep-wake-arousal cycle provided a clue. Recall that serotonin neurons are silent during REM sleep. One of the fundamental features of REM sleep is paralysis of the major muscles of the body. This is achieved by inhibiting the neurons that control the tone of the body's antigravity muscles. Might there be a relationship between the paralysis that takes place during REM sleep and the silence of the serotonin neurons?

This question was addressed with a relatively simple experiment. The destruction of a discrete part of a cat's brainstem produces an animal that by all criteria appears to enter REM sleep. However, antigravity muscle tone is present in these animals, and consequently they are capable of movement and even coordinated locomotion. (This condition has also been observed in some people who have experienced traumatic brain injuries.)

When such a cat is awake or in slow-wave sleep, the activity of its serotonin neurons is similar to that of a normal cat. When these animals enter REM

Figure 6. Experimental destruction of a discrete region in the brainstem produces an animal that reestablishes muscle tone and movement when it enters REM sleep. Unlike normal REM sleep, the animal's serotonin neurons are active and it is capable of moving about its environment. The experiment supports the hypothesis that serotonin neurons facilitate muscle activity.

Figure 7. Experimental injection of a drug that suppresses the activity of serotonin neurons in the brainstem produces a condition reciprocal to REM sleep. The cat is awake but paralyzed as it would be in REM sleep. The experiment further supports the hypothesis that serotonin neurons facilitate muscle activity.
sleep, however, instead of falling silent, the activity of the serotonin neurons increases. Cats that display the greatest amount of muscle tone and overt behavior during REM sleep also have the most active serotonin neurons. In some instances, the activity of their serotonin neurons reaches the same level as that seen during the normal waking state.

Another experiment provided further evidence for the role of serotonin neurons. When a drug that mimics the action of the neurotransmitter acetylcholine is injected into the same region of the brainstem as in the previous experiment, a condition somewhat reciprocal to normal REM sleep can be produced. These animals are awake, as demonstrated by their ability to visually track a moving object, but they are otherwise paralyzed. As in the normal animal in REM sleep, the serotonin neurons in these animals are completely silent. In association with our earlier studies, these results suggest that we are closing in on at least one of the roles played by serotonin in the brain: There is clearly a strong relationship between the activity of serotonin neurons and the body’s motor activity.

Interestingly, some serotonin neurons tend to become active just before a movement begins. Their activity may also occasionally synchronize with a specific phase of the movement—discharging most, for example, during a particular aspect of the quadrupedal stepping cycle. Moreover, the rate of the spike discharge often increases linearly with increases in the rate or strength of a movement, such as an increase in running speed or the depth of respiration.

One final observation provides a noteworthy clue to the function of serotonin neurons. When an animal is presented with a strong or novel stimulus, such as a sudden loud noise, it often suppresses all ongoing behavior, such as walking or grooming, and turns toward the stimulus. This orienting is essentially a “what is it?” response. In such instances serotonin neurons fall completely silent for several seconds, and then resume their normal activity.

Anatomical evidence supports these observations about the activity of serotonin neurons. For one thing, serotonin neurons preferentially make contacts with neurons that are involved in tonic and gross motor functions, such as those that control the torso and limbs. Reciprocally, serotonin neurons tend not to make connections with neurons that carry out episodic behavior and fine movements, such as those neurons that control the eyes or the fingers.

Our observations of the activity of serotonin neurons during different aspects of an animal’s behavior lead us to conclude that the primary function of the brain serotonin system is to prime and facilitate gross motor output in both tonic and repetitive modes. At the same time, the system acts to inhibit sensory-information processing while coordinating autonomic and neuroendocrine functions with the specific demands of

Figure 8. Serotonin neurons briefly fall silent when an animal’s attention is drawn to a novel stimulus, such as a loud noise made by a door opening or closing. At such times the animal stops all ongoing behavior, such as walking or grooming, and orients to the stimulus in a “what is it?” response. When serotonin neurons are inactive, motor output is disfacilitated and sensory-information processing is disinhibited.

Figure 9. Serotonin neurons increase their activity when an animal engages in any of a variety of repetitive behaviors such as chewing food or running on a treadmill. The rate of the action potentials also increases with the rate of the repetitive activity. Here the activity of a serotonin neuron is synchronized with a particular phase of the animal’s gait.
the motor activity. When the serotonin system is not active (for example, during an orientation response), the relations are reversed: Motor output is disfacilitated, and sensory-information processing is disinhibited.

**Brain Cells and Mental Disorders**

Although we are far from understanding the precise neural mechanisms involved in the manifestation of any mental illness, a number of studies have linked serotonin to depression. One of the most notable findings is that the major metabolite of serotonin (5-HIAA) appears to be significantly reduced in the cerebrospinal fluid of suicidally depressed patients. Our own studies suggest that serotonin neurons may be centrally involved in the physiological abnormality that underlies depression-related disorders. Recall that serotonin neurons appear to play crucial roles in facilitating tonic motor actions and inhibiting sensory-information processing. If an animal's serotonin neurons are responding abnormally, such that the rate or pattern of their activity is modified, then one might expect that both motor functions and sensory-information processing would be impaired.

Depression is frequently associated with motor retardation and cognitive impairment. If serotonin neurons are not facilitating tonic motor activity, then it should not be surprising that depressed patients feel listless and often appear to require enormous effort merely to raise themselves out of bed. Inappropriate activity during sensory-information processing might also account for the lapses of memory and the general lack of interest in the environment experienced by depressed patients. It might also be worth noting here that the well-known efficacy of REM-sleep deprivation for treating depression is at least partly dependent on serotonin. Since serotonin neurons are usually silent during REM sleep, depriving an animal of REM sleep maintains a generally higher level of activity in the system. Preliminary research in my laboratory suggests that the deprivation of REM sleep also increases the activity of serotonin neurons when the animal is in the awake state.

The activity of serotonin neurons may also be central to the manifestation of obsessive-compulsive disorders. Since our results show that repetitive motor acts increase serotonin neuronal activity, patients with this disorder may be engaging in repetitive rituals such as hand washing or pacing as a means of self-medication. In other words, they have learned to activate their brain serotonin system in order to derive some benefit or rewarding effect, perhaps the reduction of anxiety. Since the compulsive acts tend to be repeated, often to the point of becoming continuous, such activity may provide an almost limitless supply of serotonin to the brain. (The same may also be true for repetitive obsessional thoughts, but this is obviously difficult to test in animals.) Treating obsessive-compulsive disorders with a selective serotonin reuptake inhibitor ultimately accomplishes the same neurochemical endpoint, thus allowing these people to disengage from time-consuming, socially unacceptable and often physically harmful behavior.

Our studies suggest that regular motor activity may be important in the treatment of affective disorders. For example, if there is a deficiency of serotonin in some forms of depression, then an increase in tonic motor activity or some form of repetitive motor task, such as riding a bicycle or jogging, may help to relieve the depression. Indeed, there are various reports that jogging and other forms of exercise have salutary effects for depressed patients. This does not mean that exercise is a panacea for depressive disorders. Since the long-term effects of exercise on brain serotonin levels are not known, the benefits may prove to be transient. On the other hand, exercise may be an important adjunct to drug treatments.

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**Figure 10.** Major components of the hypothesized motor functions of the serotonin system are distributed in different parts of the nervous system. Excitatory (red) input from the forebrain influences the activity of serotonin neurons in the brainstem, as well as central-pattern-generating neurons and motor neurons in the brainstem and spinal cord during tonic or rhythmic motor activity. Serotonin neurons in the brainstem serve several functions: They facilitate central pattern generator and motor-neuron activity, coordinate autonomic and neuroendocrine output with motor output, and inhibit (blue) sensory-information processing.
and may permit a reduction in the required drug dosage.

Finally, there is another potentially productive avenue for drug intervention in the clinic. It is well established that the activity of serotonin neurons is under negative feedback control, in which the released serotonin molecules bind to the so-called autoreceptor on the releasing cell and acts to inhibit the cell’s activity. Because of this the administration of a metabolic precursor of serotonin, such as the amino acid L-tryptophan, cannot significantly elevate the synaptic levels of brain serotonin since neurons compensate by decreasing their activity through the negative-feedback mechanism. However, if L-tryptophan treatments are combined with low doses of an autoreceptor-blocking agent, the concentration of serotonin in the synapse might be increased without the use of serotonin reuptake inhibitors. This might prove helpful to patients who have adverse reactions to these drugs and might also circumvent the therapeutic lag of 4 to 6 weeks typically associated with antidepressants. However, because the feedback mechanism is positively correlated with the rate of serotonin neuronal activity, our results suggest that drugs that block the autoreceptor might be ineffective in quiescent, lethargic or somnolent patients. Conversely, these drugs may be most effective in active patients or those activated by artificial means.

Conclusion

Our research raises the issue of why the manipulation of a system that is primarily a modulator of motor activity has profound effects on mood. Aside from recognizing that the raphe nuclei are connected to regions of the brain that are known to be involved in the emotions (such as the limbic system), it is worth noting that a common organizational plan underlies the distribution of serotonin cell bodies and fiber terminals in essentially all vertebrate brains. This implies that the system has been conserved through evolution, and suggests that there may be some adaptive significance to linking mood and motor activity.

Consider the following possibility. We know that emotions play a role in allowing an animal to withdraw from an ongoing sequence of activities to consider alternative paths. When something bad (perhaps even life-threatening) transpires, it seems reasonable to suppress motor activity and to contemplate the available options. To put it another way: If something negative has happened in one’s world, it might be counterproductive, or even dangerous, to explore and engage the environment. The most adaptive response is to withdraw and ruminate. In this light, emotions act at a higher level of complexity in the service of effective motor behavior. When one’s mood is bright and expansive, on the other hand, it may be profitable to explore new options. Wide mood swings may allow an exploration of a broader spectrum of perspectives and thus may be related to the well-documented relationship between mood disorders and creativity in artists, writers and composers.

As a final note, the brain serotonin system may be involved in some non-clinical aspects of human behavior. Why do some people endlessly engage in rhythmic leg bouncing? What is rewarding about chewing gum? What underlies the therapeutic or reinforcing effects of breathing exercises, and the twirling or dancing movements employed by various cults and religious groups? The reader can probably think of other behaviors that increase serotonin release in his or her brain.

Bibliography


