The Wisdom of the Receptors: Neuropeptides, the Emotions, and Bodymind

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What connects emotion to physiology? How does the mind communicate with the body, the body with the brain? In this article, Candace Pert, Chief of Brain Biochemistry in the Clinical Neuroscience Branch at the National Institute of Mental Health, explores the compelling, central question of how the body communicates with itself. For Pert the body's "information system" has two major elements-the chemical substances known as neuropeptides and the receptors into which they fit. Neuropeptides are produced by nerve cells in the brain, and when they lock into their receptors, which are attached to other cells in the body, they make something happen (or prevent it from happening). By examining recent findings (many of them from her laboratory) on the "messages" of individual neuropeptides, how they get to their appropriate receptors, the location of the receptors on different cells, the function and mobility of these cells, Pert outlines a new view of the body's internal conversation, a conversation that appears to be remarkably flexible, varied, and subtle. For example, certain immune cells carry all the receptors identified so far, which means, presumably, that they can be affected by a wide range of "messenges." 'I'hese findings lead Pert to a series of provocative conclusions, among them that mind and body~ bound together, as it were, by the talk of the neuropeptides, are best understood as an integrated entity that she calls "Bodymind."-Ed.

In this talk, I am going to describe an array of fascinating, mostly new findings about. the chemical substances in the body called neuropeptides. Based on these findings, I am going to suggest that neuropeptides and their receptors form an information network within the body. Perhaps this suggestion sounds fairly innocuous, but its implications are far reaching. I believe that neuropeptides and their receptors are a key to understanding how mind and body are interconnected and how emotions can be manifested throughout the body. Indeed, the more we know about neuropeptides, the harder it is to think in the traditional terms of a mind and a body. It makes more and more sense to speak of a single integrated entity, a "bodymind." Most of what I will describe are laboratory findings, hard science. But it is important to recall that the scientific study of psychology traditionally focuses on animal learning and cognition. This means that if you look in the index of recent textbooks on psychology, you are not likely to find "consciousness," "mind," or even "emotions." These subjects are basically not in the realm of traditional experimental psychology, which primarily studies behavior because it can be seen and measured. What goes on in the so- called black box of the brain/mind, B. F. Skinner has maintained, is not something to be speculated about. It cannot be observed, and so its study is not hard science.

One of the things I can report today is that the realm of laboratory research has widened enormously. My findings come from the domain of hard science, and I believe they are directly relevant to the comprehension of emotions and even open a window into the black box of the mind.

The Specificity of Receptors

Now, there is one area where mind-at least consciousness-has been objectively studied for perhaps twenty years as a part of psychology, and that is the area of psychopharmacology. People have thought of highly rigorous ways to measure the effects of drugs and altered states of consciousness.

Pharmacology evolved talking about how no drug acts unless it is fixed- that is, somehow gets attached to the brain-and people imagined hypothetical tissue constituents that they called receptors. In this way, the notion of specific receptors became a central theory in pharmacology. It is a very old idea. In the past several years, the critical development for the study of receptors has been the invention of new technologies for actually binding drugs to these molecules and for studying both their distribution in the brain and body and their actual molecular structure.

My initial work in this area was in the laboratory of Solomon Snyder at Johns Hopkins, and we focused our attention on opium, a drug that obviously alters consciousness and that also is used medicinally, to alleviate pain. I worked long and hard, over many months of failure, to develop a technical system for measuring the material in the brain with which opium interacts to produce its effects. To make a long (and technical) story short, we used radioactive drug molecules, and with this technology were able to identify the receptor element in the brain. You can imagine a molecule of opium attaching itself to a receptor much as a key fits into a lock- and then from this small connection, large changes follow.

It next turned out that the whole class of drugs to which opium belongs-they are called opiates (or opioids), as you probably know, and they include morphine, codeine, and heroin, as well as opium-attach to the same receptors. Further, we discovered that the receptors were scattered throughout not only the brain but also the body.

I might mention that each opiate is slightly different in its shape and binds more or less tightly to the receptor molecules. For instance, the reason a person does not get the tremendous rush from codeine that comes with heroin is that heroin bas blobs of molecular matter that allow it to course into the brain while codeine first has to be transformed into morphine in the liver. Morphine, for its part, penetrates the brain, where euphoria receptors are located, very poorly. After finding the receptor for the external opiates, our thinking took another step. If the brain and the other parts of the body have a receptor for something taken into the body called an exogenous ligand-it makes sense to suppose that something produced inside the body-an endogenous ligand-also fits the receptor. Otherwise, why would the receptor be there? This perspective ultimately led to the identification of the brain's own form of opiates- or, rather, one of them. This is a chemical substance called beta-endorphin. With beta-endorphin we come to the first of the neuropeptides- which are simply peptide structures produced by nerve cells in the brain. Beta-endorphin is created in nerve cells, it chemically is a peptide, so it is a neuropeptide. Perhaps I should explain that peptides are strings of amino acids, and as you may know, there are sixteen main amino acids and every peptide or protein in the body is made out of these sixteen amino acids strung out and arranged in different sequences. You can think of the amino acids as 16 different colored beads, and they allow for an almost infinite number of sequences. Different sequences produce different chemicals, some of which are neuropeptides. In the case of beta-endorphin, we now know its precise sequence of amino acids. I want to mention in passing that

beta-endorphin is found in very large quantities in the human pituitary gland, which of course is part of the brain, and recently it has been shown to be in the gonads as well. Brain and body. We will come back to this point later.

Now, it is quite exciting that the endogenous ligands for the opiate receptors turn out to be peptides because peptides come directly from the DNA (via mRNA). There is no enzyme in between, they derive directly from DNA, which stores the information to make our brains and bodies. If you picture an ordinary nerve cell, you can visualize the general mechanism. In the center (as in any cell) is the nucleus containing the DNA, and a direct printout of the DNA leads to the production of a neuropeptide, which then traverses down the axons of the nerve cell to be stored in little vesicles at the end waiting for the right electro-physical events that will release it. The DNA also has the information that codes for the receptors, which are made out of the same peptide material (amino acids) but are much bigger. Beta endorphin has 31 amino acids, but the human opoid receptor for example turns out to have about 500 amino acids.

What has to be added to this picture is the fact that 50 to 60 neuropeptides have been identified, each of them as specific as the beta-endorphin neuropeptide. In other words, the DNA produces all these neuropeptides, which all traverse down axons and all wait for the right electro·physical events. We have here an enormously complex system which is kept straight by the high specificity of the neuropeptides and their receptors.

Until quite recently, it had been thought that the information in the nervous system was distributed across the gap between two nerve cells, called synapses. We all learned about synapses in high school biology. The notion was that one nerve cell communicated to another across a synapse, which meant that the proximity of the nerve cells determined what could be communicated. Now we realize that synapses are not as important as we thought. They help control some kinds of information flow, particularly muscle contraction. But the largest portion of information coming from the brain is kept straight not by the close physical juxtaposition of nerve cells, but by the specificity of the receptors. What was thought of as a highly rigid linear system appears to be one with far more complex patterns of distribution.

When a nerve cell squirts out opiate peptides, the peptides can act “miles" away at other nerve cells. The same is true of all neuropeptldes. At any given moment, many neuropeptides may be floating along within the body, and what enables them to attach to the correct receptor molecules is, to repeat, the specificity of the receptors. Thus, the receptors serve as the mechanism that sorts out the information exchange in the body.

The Biochemistry of the Emotions

What is this leading up to? To something very intriguing-the notion that the receptors for the neuropeptides are in fact the keys to the biochemistry of emotion. In the last two years the scientists in my lab have formalized this idea in a number of theoretical papers[1], and I am going to briefly review the evidence to support it.

I should say that some scientists might describe this idea as outrageous. It is not, in other words, part of the established wisdom. Indeed, coming from a tradition where the textbooks do not even

contain the word "emotions" in the index, it was not without a little trepidation that we dared to start talking about the biochemical substrate of emotions.

I will begin by noting a fact that neuroscientists have agreed on for a long time: that emotions are mediated by the limbic system of the brain. The limbic system refers to a section of neuroanatomical parts of the brain which include the hypothalamus (which controls the homeostatic mechanisms of the body and is sometimes called the "brain" of the brain), the pituitary gland (which regulates the hormones in the body), and the amygdala. We will be talking mostly about the hypothalamus and the amygdala.

The experiments showing the connection between emotions and the limbic system were first done by Wilder Penfield and other neurologists who worked with conscious, awake individuals. The neurologists found that when they used electrodes to stimulate the cortex over the amygdala they could evoke a whole gamut of emotional displays-powerful reactions of grief, of pain, of pleasure associated with profound memories, and also the total somatic accompaniment of emotional states. The limbic system therefore was first identified by psychological experiments.

In 1975 we began to map the location of opiate receptors in the brain-by a method involving binding of radioactive molecules to slices of brain tissue. The density of these radioactive molecules, as they accumulate in the opiate receptors in different spots of the brain, can be transformed into a quantitative color scale, like weather maps. We found that the limbic system was highly enriched with opiate (and other neuropeptide receptors too, we subsequently learned). The amygdala and hypothalamus, both classically considered to be the main components of the limbic system (the great physiologist, Walter B. Cannon, singled out the hypothalamus as the foremost area for emotions to hook up to the brain), are in fact blazing with opiate receptors-40-fold higher than in other areas in the brain. These hot spots
correspond to very specific nuclei or cellular groups that physiological psychologists have identified as mediating such processes as sexual behavior, appetite, and water balance in the body. The main point is that our receptor-mapping confirmed and expanded in important ways the psychological experiments that defined the limbic system. We were able to overlay a biochemistry of specific neuropeptides to brain regions implicated in the expression of emotions and behaviors.

Let me back track a moment and bring in some other neuropeptides. I have already noted that 50 to 60 substances are now considered to be neuropeptides. Where do they come from? Many of them are the natural endogenous counterparts of psychoactive drugs. But another major source-very unexpected-are the hormones. Hormones historically have been conceived of as being produced by glands-in other words, not by nerve cells. A hormone presumably was stored in one place in the body, then travelled over to its receptors in other parts of the body. A prime example of a hormone is insulin, which is secreted in the pancreas. But, now, it turns out that insulin is not just a hormone. I fact, insulin can be a neuropeptide, made and stored in the brain, and there are insulin receptors in the brain as well. When we map insulin in brain, we again find hot spots in the amygdala and hypothalamus. In short, it has become increasingly clear that the limbic system, the classical seat of emotions in the brain, is also the focal point of receptors for neuropeptides, some of which were first identified as hormones.

Another critical point. As we have studied the distribution of these receptors, we have found that the limbic system is not just in the forebrain, in the classical locations of the amygdala and the hypothalamus. It appears that the body has other places in which many different neuropeptide receptors are located- places where there is a lot of chemical action. We have call these hot spots "nodal points", and they are anatomically located at places that receive and process a lot of emotional information. One nodal point is the dorsal (back) horn of the spinal cord, which is the place that sensory information enters the central nervous system. This is the first synapse within the brain where touch-sensory information is processed. We have found that for virtually all the senses for which we know the entry area, this location is always a nodal point for neuropeptide receptors.

I believe these findings have amazing implications for understanding and appreciating what emotions do and what they are about. Consider the chemical substance angiotensin, another classical hormone which is also a peptide and now shown to be a neuropeptide. When we map the angiotensin receptors in the brain, we again find little hot spots in the amygdala. It has long been known that angiotensin mediates thirst, so if one implants a tube in the area of a rat's brain that is rich with angiotensin receptors and drops a little angiotensin down the tube, within 10 seconds, the rat will begin to drink water, even if it is totally sated with water. Chemically speaking, angiotensin translates as an altered state of consciousness, a state that makes animals (and humans) say, "I want water". In other words, neuropeptides bring us into states of consciousness, states of feeling, states of emotion, and states of behavior. And to alterations in those states.

For another example, we have in the laboratory mapped the receptors for PCP (commonly referred to as "angel dust"), a. drug of abuse that induces an altered state of consciousness. Using radioactive PCP, we have shown that the receptors tend to be in the brain cortex, and with rats as our subjects, we have been able to determine (using the technique of operant animal behavior) that we are in fact measuring the peptide molecules of PCP that are responsible for an altered state of consciousness.

Equally important is the fact that neuropeptide receptors are not just in the brain, they are also. in the body. We have mapped and shown biochemically that there are angiotensin receptors in the kidney identical to those in the brain, and in a way that is not yet quite understood, the kidney located receptors conserve water in the body. We know that they play with the ion fluxes so that water is conserved. The point is that the release of the neuropeptide angiotensin leads both to the behavior of drinking and to the internal conservation of water. Here is an example of how a neuropeptide-which perhaps corresponds to a mood state-can integrate what happens in the body with what happens in the brain. (A further important point that I mention here is that overall integration of behavior with brain and body biochemisty seems designed to promote and optimize survival.)

My basic speculation here is that neuropeptides provide the physiologic basis for the emotions. As my colleagues and I argued in a recent paper in the *Journal of Immunology* (1985): The striking pattern of neuropeptide receptor distribution in mood-regulating areas of brain, as well as their role in mediating communication throughout the whole organism, makes neuropeptides the obvious candidates for the biochemical mediation of emotion. It may be too that each neuropeptide biases information processing uniquely, when occupying receptors

at nodal points with the brain and body. If so, then each neuropeptide may evoke a unique "tone" that is equivalent to a mood state.

In the beginning of my work, I matter-of-factly presumed that emotions were in the head or the brain. Now I would say they are really in the body as well. They are expressed in the body and are part of the body. I can no longer make a. strong distinction between the brain and the body.

Communicating with the Immune System

I now want to bring the immune system into this picture. I have already explained that the hormone system, which historically has been studied as being separate from the brain, is conceptually the same thing as the nervous system. Splashes of neuropeptide juices are released and diffuse very far away, acting via the specificity of the receptors at sites far from where the juices are stored and released. So, endocrinology and neuroscience are two aspects of the same process. Now I am going to maintain that immunology is also part of this conceptual system and should not be considered a separate discipline. A key property of the immune system is that its cells move. The brain of course is stable. It stays in one place. The cells of the immune system-although they are identical to the cells of the brain with their little nuclei, their cell membranes, and their varied receptors-move around. Monocytes, for example, which ingest foreign organisms, start life in your bone marrow, and they then diffuse out and travel through your veins and arteries, and decide where to go by following chemical cues. A monocyte travels along in the blood and at some point comes within "scenting" distance of a signaling peptide, and because the monocyte has receptors for that peptide on its cell surface, it begins literally to chemotax, or crawl, along that chemical gradient. This is very well documented, and there are excellent ways of studying it in the laboratory.

Now, monocytes are responsible not just for recognizing and digesting foreign bodies but also for wound healing and tissue-repair mechanisms. For example, they have enzymes that produce and degrade collagen, an important structural material out of which the body is made. What we are talking about, then, are cells with vital, health-sustaining functions.

The new discovery I want to emphasize here is that every neuropeptide receptor that we have looked for (using an elegant and precise system developed by my colleague, Michael Ruff) Is also on human monocytes. Human monocytes have receptors for opiates, endorphins, for PCP, for another peptide called oxytocin, and so on. These emotion-affecting biochemicals actually appear to control the routing and migration of monocytes, which are so pivotal in the immune system. Monocytes turn into the tissue macrophages that control repair processes, they communicate with B-cells and T-cells to cause immunity, indeed interact in the whole system to fight disease and distinguish between self and non-self, deciding, say, which part of the body is a tumor cell to be killed by natural killer cells, and which parts need to be restored. I hope this picture is clear to you. A monocyte is a circulating, health-sustaining element of the immune system, that travels in the blood, and then the presence of a peptide pulls it over, makes it stick to the blood vessel wall, where it then crawls into the tissue or organ. It can connect with the neuropeptide because it has the receptor to do so-it has, in fact, many different receptors for different neuropeptides and other immune peptides.

It turns out, moreover, that the cells of the immune system not only have receptors for these

various neuropeptides, as is becoming clear, they also make the neuropeptides themselves. There are subsets of immune cells that make beta endorphins, for example, and the other opiate peptides. In other words, they are making the same chemicals that we conceive of as controlling mood in the brain. They control the tissue integrity of the body, and they also make chemicals that control mood. Once again, brain and body act as one.

I want to emphasize the point that the same receptors are in the brain and in the immune system. CCK, another neuropeptide, was first sequenced and discovered by its action on the gut. In the pharmacological beginnings of the search for receptors, people would string up gut muscles in organ baths and study their contractions. Since the gut contained functional receptors, it was used to isolate and determine the chemical structures of the bioactivity in tissue extracts. It turns out that CCK is highly involved with food satiety. Doses of CCK make you not want to eat any more. We have recently shown that both the brain and the spleen- which can be described as the “brain” of the immune system-contain receptors for CCK. So brain, gut, and immune system can all be affected by CCK.

What do these kinds of connections between brain and body mean? Often they are referred to as "the power of the mind over the body." As far as I am concerned, that phrase does not describe what we are talking about here. The body in these experiments is the outward manifestation of the mind. I would go further. When we document the key role that the emotions, expressed through neuropeptide molecules, play in affecting the body, it will become clear how emotions can be a key to the understanding of disease.

I want to expand on this speculation by re-turning to the example of the gut. The entire lining of the intestine, from the esophagus through the large intestine is lined with cells, nerve cells and other kinds of cells-that contain neuropeptides and neuropeptide receptors. It seems entirely possible to me that the richness and diversity of the receptors may be why a lot of people feel their emotions in their gut-why they have a "gut feeling."

We are all aware of the bias built into the western idea that consciousness is totally in the head. I believe the research findings I have described indicate that we need to start thinking about how consciousness can be projected into various parts of the body. Unfortunately, people who think about these things do not usually work in a Government laboratory.

Let me summarize the basic idea I have been developing. My argument is that the three classic disciplines of neuroscience, endocrinology, and immunology, with their various organs-the brain (which is the key organ that the neuroscientists study), the glands, and the immune system (consisting of the spleen, the bone marrow, the lymph nodes, and of course the distributed cells throughout the body)-that these three areas are actually joined to each other in a bidirectional network of communication and that the information “carriers" are the neuropeptides. There are well-studied physiological substrates showing that communication exists in both directions for every single one of these areas and their organs. Some of the research is old, some of it is new. We now know, for example, that peptide-producing neurons come from the brain and actually enervate the bone marrow.

The word I would stress in regard to this integrated system is “network”, which comes from information theory. What we have been talking about all along is information. In thinking about these matters, then, it might make more sense to emphasize the perspective of psychology rather than of neuroscience. For the term *psycho* clearly conveys the study of mind, and perhaps mind is the information flowing among all of these bodily parts, and that may be what mind is. A mind is composed of information, and it has a physical substrate, which is the body and the brain, and it also has another immaterial substrate that has to do with information flowing around. Maybe mind is what holds the network together.

The Unity of the Variety

The last point I am going to make about the neuropeptides is an astounding one I think. As we have seen, neuropeptides are signaling molecules. They send messages all over the body (including the brain). Of course, to have such a communications network, you need components that can talk to each other and listen to each other. In the situation we are discussing here, the components that “talk” are the neuropeptides, and the components that "hear" are the neuropeptide receptors. How can this be? How can 50 to 60 neuropeptides be produced, float around, and talk to 50 or 60 types of listening receptors which are on a variety of cells? Why does order rather than chaos reign? It has to do with the specificity, the selectivity of the receptors, not their direct wiring, not neuron to neuron.

I note in passing that the receptors are quite capable of changing their conformations within the cell membranes, which can occur at a very rapid pace-so rapid that it’s hard to tell whether it is in one state or another at a given moment in time. In other words, receptors have both a wave-like and a particle character, and it is important to note that information can be stored in the form of time spent in different states.

As I said, the molecular unity, the conservation receptor structure is quite amazing. Consider the tetrahymena, a protozoa that is one of the simplest organisms. Despite its simplicity the tetrahymena can do almost everything we can do. It can eat, have sex, and of course it makes the same neuropeptide components that I have been talking about. The tetrahymena makes insulin. It makes beta endorphin-like peptides. The actual molecule for the rat-brain opiate receptor is highly similar to the human-brain opiate receptor and is also identical to the opiate receptor-components in that simplest of animals. I hope the force of this is clear. The opiate receptor in my brain and in your brain is, at root, made of the same molecular substance as more primitive creatures.

This finding gets to the simplicity and the unity of life. It is comparable to the four DNA based pairs that code for the production of all the proteins, which are the physical substrates of life. We now know that in this physical substrate there are only 60 or so signal molecules, the neuropeptides, that account for the physiological manifestation of emotions-for enlivening emotions, if you will, or perhaps better yet, for flowing energy. Nearly identical molecular components for information flow are conserved throughout evolution. The whole system is simple, elegant, and it may very well be complete.

Is the Mind in the Brain?

We have been talking about mind, and the question arises: Where is It? In our own work, consciousness has come up in the context of studying pain and the role of opiate receptors and endorphins in modulating pain. A lot of labs are measuring pain, and we would all agree that the area called periaqueductal gray, located around the third ventricle of the brain, is filled with opiate receptors, making it a kind of control area for pain. We have found that the periaqueductal gray is also loaded with receptors tor virtually all the neuropeptides that have been studied.

Now, everyone knows that there are yogas who can train themselves so that they do or do not perceive pain, depending on how they structure their experience. There are other people, called mothers, who have done the same thing. What seems to be going on is that these sort of people are able to plug into their periaqueductal grey. Somehow they gain access to it with their consciousness, I believe- and set pain thresholds. Note what is going on here. In these situations, a person has an experience that brings with it pain, but a part of the person consciously does something so that the pain is not felt. Where is this consciousness coming from-this conscious I- that somehow plugs into the periaqueductal gray so that he or she does not feel a thing?

I want to go back to the idea of a network. A network is different from a hierarchical structure which has one top place. You theoretically can plug into a network at any point and get to any other point. A concept like this seems to me valuable in thinking about the processes by which a consciousness can manage to reach the periaqueductal gray and use it to control pain. The yoga and the laboring woman both use a similar technique to control pain, breathing. Athletes use it, too. Breathing is extremely powerful. I suggest that there is a physical substrate for these phenomena, the brain stem nuclei. I would say that we now must include the brain stem nuclei in the limbic system because they are nodal points, thickly encrusted with neuropeptide receptors and neuropeptides. The idea, then, goes like this: breathing has a physical substrate which is also a nodal point, this nodal point is part of an Information Network in which each part leads to all the other parts, and so, from the nodal points of the brain stem nuclei, the consciousness can, among other things, plug into the periaqueductal gray.

I think it is possible now to conceive of mind and consciousness as an emanation of emotional information processing, and as such, mind and consciousness would appear to be independent of brain and body. One little hint about how the mind might send its information through the brain and body is suggested by another astounding fact. It is well established in experimental work that some of the monocytes which arise in the bone marrow and circulate around, then actually enter the brain and are transformed and become glial cells. What are glial cells? They have been generally ignored by neuroscientists in favor of the neurons. They are ten times more plentiful in the brain than nerve cells. People say, "They're nutritive," or "They clean up." They have not been studied much because they do not have measurable electric properites. (A lot of neuroscience has been based on the ability to measure electrical epiphenomena) It is possible that glial cells have the potential to be programmed in the brain and under the appropriate cues to leave the brain and go out into the body. Also, there is a precedent for monocyte-like cells, which contain information about the state of the body, to take up residence in- and talk directly to-the brain. Perhaps that is one mechanism of action by which the mind and body intercommunicate.

One last speculation, an outrageous one perhaps, but on a theme I was asked to consider for this symposium on “Survival and Consciousness”. Can the mind survive the death of the physical brain? Perhaps here we have to recall how mathematics suggests that physical entities can suddenly collapse or infinitely expand. I think it is important to realize that information is stored in the brain, in the body, in the BodyMind, and it is conceivable to me that this information could transform itself into some other, non-material realm. The DNA molecules surely have the information that makes the brain and body, and the bodymind shares the information molecules that enliven the organism. Where does the information go after the destruction of the molecules (the mass) that compose it. Matter (energy) can neither be created nor destroyed, and perhaps biological information flow does not just disappear at the moment of death but is transformed into another realm. Who can rationally say "impossible"? No one has yet mathematically unified gravitational field theory with matter and energy. The mathematics of consciousness have not even been approached. The nature of the hypothetical "other realm" is currently in the religious or mystical dimension, where Western science is clearly forbidden to tread.

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Reference

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