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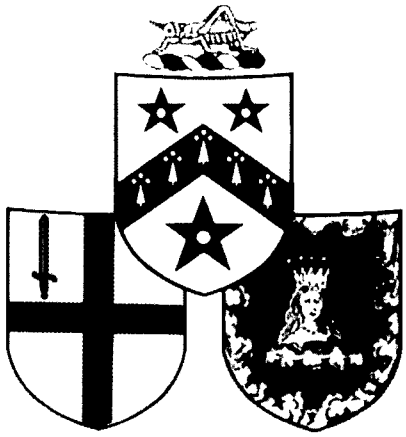

EXPLORING THE BRAIN

Lecture 2

LITTLE GREY CELLS

by

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6 December 1995

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GRESHAM LECTURE 2:

LITTLE GREY CELLS

The brain is made of 'brain tissue'. Brain tissue normally has the consistency of a soft boiled egg, and is a kind of creamy colour. However by looking at it with the naked eye, it would be impossible to guess what brain tissue was composed of. Even if you cut a thin slice of it and placed it on a glass slide to look at it under the microscope, you would still see effectively nothing.

Such was the problem confronting Camillo Golgi, an Italian who worked at Pavia University over a hundred years ago. In 1872, he made a great advance: one day, so the story goes, he knocked by accident a block of brain into a dish containing a solution of silver nitrate, where it remained lost for several weeks. It turned out that just by sheer chance Golgi had 'discovered' the critical step. We now know that once brain tissue has been placed in silver nitrate for a minimum of three hours, then it possible to visualise the components of brain tissue: nerve cells or 'neurons'.

What do neurons actually look like? In all cases there is a squat, blob-shaped region known as the 'cell body' or, again from the Greek for body, 'soma'. The diameter of this blob-like body is some forty thousandths of a millimetre. Actually, the shape of the soma is usually not as ambiguous and amorphous as the term blob implies, but can come

in any one of several characteristic shapes, such as round, oval, triangular or 'fusiform' (shaped like a spindle). The cell body contains all the life-support organs for the neuron, and in this regard neurons are no different from any other cell in your body. However, there is a very big difference between neurons and other cells that can be appreciated just by looking at their respective shapes.

But there is more to a neuron than just the cell body. Arising from this body are what appear to be mini branches. It is no exaggeration to say that these branches coming out of the neuron looks a little like a tree. If fact, this part is named after the Greek for tree, 'dendrites'. Just like real trees, the dendrites of a neuron can take on all number of overall shapes, vary in density and emanate from all around the neuron, giving it a star-like appearance, or alternatively just sprout out from one or booth ends of the cell body. Unlike other cells, neurons not only have these mini-branches, dendrites, but in addition most have a very long, thin fibre stretching out from the cell body that is many times longer than the rest of the neuron. The normal range for diameter of a cell body is some twenty to one hundred thousandths of a millimetre: however in the most extreme case a fibre, such as one running down the spinal cord, can be up to a metre long! This fibre is called an 'axon'. These long thin axons stretch out over such long distances because it is via these long connections that they are able to communicate with each other. It is the ability for communication in this way that makes neurons very different from all other cells in the body.

Neurons communicate with each other by sending an electrical signal. As well as ions amassing inside and outside of the neuron, there are also other negatively charged proteins, large molecules inside the cell: taking everything into consideration, the distribution of charge that results either side of the neuronal membrane turns out to be uneven, there is not an equal number of plusses and minuses. The final effect of this uneven distribution of charge is that the inside is negative with respect to the outside of the neuron and there is thus a 'potential difference', a voltage across the cell, in the order of hundredths of a volt.

But there is little point in having this potential difference if it was never possible for the ions to flow, to have a real electric current. It would be a bit like having a dam that had enormous reserves of water stacked up on one side, which you were nonetheless never able to use. So for a cell to generate an electrical signal, a current has to flow. In order for the current to flow, the ions need, temporarily, to be able to come in and go out of the neuron.

The principal electrical signal of a neuron occurs when positively charged sodium ions are briefly able to enter the cell, making the voltage temporarily positive: thereafter positively charged potassium ions leave the cell, making the voltage temporarily more negative to normal. Hence when the neuron is activated in this way, there is a brief and characteristic change in the potential difference, a positive pulse, followed by a negative overshoot: this transient positive-negative wave

lasts most usually for about one or two thousandths of a second and is known as an 'action potential'.

An action potential for any given neuron is always the same size, but as the incoming signals becomes more numerous or stronger, then the receiving neuron is said to become more 'excited', and as a result it will generate more and more action potentials. Action potentials never change in their amplitude for any particular cell: the way a neuron signals more or less vigorously is always by a change in the frequency of action potential generation. The speed at which the electrical signal, the action potential, is transmitted varies according to the diameter of the axon and whether or not it is insulated with a fatty sheath known as 'myelin'. In the disease of multiple sclerosis parts of the myelin sheath deteriorates and so certain nerves start conducting electrical signals less efficiently than otherwise. In any event, nerve conduction is very fast: it can be up to about 220 miles per hour!

We now know that this contact is a gap, a 'synapse', so narrow that it is only visible when magnified over ten thousand times. But the concept of the synapse immediately presents a problem. Just imagine that a signal, an electrical impulse travelling at some 220 miles per hour, arrives at the end of the axon, and hence at the synapse. True, the end of axon (the 'axon terminal') is now excited, the potential is briefly more positive. But where is this wave of excitation, this impulse going to go? How can it be used as a signal to another neuron when it is kept at bay by a gap? It is a little like driving in a car and coming to a river. What

one would have to do is abandon the car and find a more appropriate means of travel, a boat. We need a way of translating the electrical signal into one that can cross the synapse.

Once the action potential, the electrical signal, invades the end of the axon, it creates the right conditions by which a chemical referred to as a 'transmitter' is released from small packets within the nerve, into the synapse. The requisite condition which triggers the emptying of the small packets of transmitter into the synapse is a change in voltage, the transient positive potential difference brought about by the arrival of the action potential. The more electrical signals arriving, the more chemical will be released. In this way the original electrical signal is converted accurately into a chemical one, where the intensity of the signal is preserved.

Once released, the transmitter diffuses easily through the watery, salty liquid outside all neurons (the extracellular fluid), crossing the synapse as readily as a boat might cross a river. The time scales are vastly different however: since such chemicals are relatively small molecules, the gap is crossed within thousandths of a second. But how does a chemical, a mere molecule actually transmit a 'message'?

Each molecule of the transmitter chemical binds to another class of special protein on the outside of a neuron: these special proteins, which are called 'receptors', are tailor-made for a specific chemical as precisely as a key is made for a lock. A receptor will not just let any old chemical

dock into it, it has to be a special one where the molecular configuration is a perfect fit. Once the transmitter is locked into the receptor and bound to it, then the creation of effectively a new chemical, a 'complex' of the original two molecules, acts as a trigger for a special series of events to unfold.

The inter-locking of the transmitter molecule with the receptor protein on the target cell causes ion channels in that target cell to open: there is now therefore a transient change in potential difference in the target cell. In this narrative of how cells communicate, we have now, in a sense, come full cycle. This change in potential difference becomes just one of the many electrical signals we saw at the outset were conducted down the dendrites towards the cell body. Once at the cell body, this particular signal will contribute, along with many other incoming signals, to a final net change in voltage in the target cell. Once again, if the net change in voltage is sufficiently marked, then the voltage requirements will be met for opening sodium channels in the cell body and instigating an action potential in this new target cell, which will itself then send a signal to become one of thousands impinging on the next target cell along, and so on, in a repeating sequence of electrical and chemical events.

A final advantage, although not one expressly designed by Nature, is that if we have specific transmitter chemicals acting in this way on highly specific receptor protein molecules, then either the transmitters themselves or their receptor protein targets can be targeted by particular

compounds, drugs. Since we know that drugs can change the way we think and feel both as therapy and as substances of abuse, we can see how to change how specific neurons are communicating with each other: hence we can truly savour the surreal thought that what we regard as an individual and unchanging mind, is completely at the mercy of our physical brain, our neurons.

One drug that works as a caricature of a natural transmitter, is morphine. Morphine mimics a naturally occurring transmitter that we have in our body, 'endorphin'. Morphine is of a sufficiently similar molecular configuration to fit readily into the receptor protein that is custom-made for these endorphins. It can thus fool the target neuron that it is being activated by its normal, chemical messenger, endorphin. It was a great discovery in the 1970s that we have these natural agents in our body that work, to signal between certain neurons. Moreover at least some of this endorphin-mediated signalling appears important for relieving pain: for example, we know that if the action of endorphins are blocked by a drug, naloxone, then our perception of pain is worse. Along the same lines, naloxone also prevents at least some of the analgesic effects of acupuncture.

Just because we have a naturally occurring morphine/heroin analogue in our brains, does not mean to say we are all at risk of becoming drug addicts. These endorphins will be released in different places in the brain at different times, and in small amounts. When a drug is taken however, such as morphine itself, then it will act on all possible

brain areas at once, at each and every respective synapse: it will swamp the normal receptor sites. The consequences of such excessive activation of the receptor site is that it becomes accustomed to these higher amounts of chemical and thus far less sensitive to normal amounts. This process of 'down regulation' continues until more and more drug is required to have the same initial effects. This is one important factor in addiction.

Drugs can also modify neuronal communication by influencing transmitter synthesis, release and availability. For example, the drug given to Parkinsonian patients, L-DOPA, acts to increase the availability of the transmitter dopamine, which is low in certain brain regions in that disease. But we still do not understand why dopamine is needed for normal movement. The brain is built up from single neurons in increasingly complex circuits. Between ten thousand to one hundred thousand neurons make contact with any particular neuron at any particular time. In turn, any particular neuron will become one of many thousands of inputs for the next cell in the network. It is therefore important not to extrapolate directly from an event at the single synapse, to a 'function' of the brain.