Wellcome Film Project

Neurological Basis of Reward

The Scientific Basis of Medicine

Presented by Dr TJ Crow, Clinical Research Centre, Northwick Park Hospital.

University of London Audio-Visual Centre, 1975.

Produced by Trevor A Scott.

Made for British Postgraduate Medical Federation.

Black and White
Duration: 00:24:51:03

00:00:00:00

<**Dr TJ Crow to camera**>

Jeremy Bentham, the philosopher, held the belief that man has two sovereign masters, pain and pleasure. It is to them alone, he suggested, to determine what we shall do. The functions of pain are clear enough – an organism which does not avoid potentially damaging stimuli is at an obvious disadvantage. The biological value of reward is more illusive. Two distinct concepts have been developed. The first is the rewarding stimuli in some way activate the organism toward biologically significant features of the environment. Thus the smell or sight of food will have the effect of orientating and activating the organisms motive behaviour towards food. Such stimuli are said to act as incentives. Secondly, rewarding stimuli can act as reinforcers, that is, they may influence the course of learning. According to this view, behaviours which are followed by a biological reward, say, food, become more firmly fixed in the organism's behavioural repertoire. The rewarding stimulus signals the success of a particular behavioural sequence and ensures that that sequence is retained.

In 1956, Olds and Milner opened up a neurophysiological approach to the mechanisms of reward. They discovered that with electrodes implanted in certain brain sites, rats could be trained to press a lever to deliver stimulation to their own brains.

<**Crow over short film showing a rat with electrodes implanted in its brain, stimulating reward mechanism when it presses levers**>

Here is a rat and a standard operant conditioning apparatus. Each lever press activates a stimulator which delivers a train of electrical pulses through the implanted electrode. This behaviour can occur at high rates and persists for long periods of time. In some cases, lever pressing from electrical reward overrides other biological needs – for example, a thirsty rat will continue to lever press for electrical reward rather than drink when water's available. It appears that the electrode must be activating powerful central reward mechanisms.

<**End of film clip**>

<**Crow over diagram showing which areas of a rat's brain respond to electrical self-stimulation**>

Which are the sites from which electrical self-stimulation can be obtained? Here is a diagram of a rat brain, extending from the olfactory bulbs on the left to the brain stem and cerebellum on the right. Early in these investigations it was shown that the self-stimulation sites correspond quite closely to the distribution of the medial forebrain bundle. This large bundle of fibres travels through the general region of the lateral hypothalamus, from olfactory bulbs to ventral midbrain. Anatomically it consists of small diameter fibres and, for this reason, is somewhat ill defined. Some fibres travel rostrally and some caudally and their nuclei of origin are, in many cases, unidentified. Therefore, the direct anatomical approach to the neural mechanisms of reward made limited progress.

<**Crow to camera, then over table showing drugs which have an effect on neuronal reward mechanisms, then back to camera**>

In 1963, Stein introduced the idea that the central mechanisms of reward could be identified in chemical terms by way of the neurotransmitters released by the reward pathways. He pointed out that the effects of various drugs are those which would be expected if the pathways involved released a catecholamine; he suggested noradrenaline, as a neurohumor. Several observations are consistent with this hypothesis. For example, the drugs, the amphetamines and cocaine, drugs which enhance the release of catecholamines from central amine neurones, facilitate self-stimulation responding. Secondly, reserpine and tetrabenazine, drugs which deplete central monoamine stores, including catecholamines, inhibit self-stimulation responding. And the drug alpha-methyl-para-tyrosine, which selectively inhibits the synthesis of catecholamines, has also been shown to depress self-stimulation responding. Finally, the interesting compound 6-hydroxydopamine, a drug which when administered intraventricularly or intracerebrally causes a selective degeneration of central catecholamine neurones, also has been shown to inhibit self-stimulation responding.

There is, therefore, an a priori case for an association between central catecholamine neurones and reward processes. However, these findings could also be explained if central catecholaminergic mechanisms, or noradrenergic mechanisms, had some facilitatory effects on behaviour in general. To test the catecholamine hypothesis of reward, some more direct approach to the relationship between reward mechanisms and central catecholamine neurones is required. Where, for example, are the catecholamines in the brain? The answer to this question comes from an extensive series of studies using the Falck-Hillarp technique.

00:05:47:00

<**Crow over diagram showing application of Falck-Hillarp technique to study of catecholamine systems in the rat brain**>

With this technique it's possible to study the distribution of catecholamines in the brain at a microscopic level. This diagram represents the location of the major ascending catecholamine systems in the rat brain. They arise mainly from a series of cell body groups located in the brain stem. There are three major systems. Firstly, a large system of dopamine-containing neurones arising from the ventral midbrain. These give rise to fibres travelling up through the lateral hypothalamus to be distributed to the entire corpus striatum and to some related nuclei. Secondly there are two major systems of noradrenaline neurones. Firstly, the dorsal bundle of noradrenaline neurones arising from a small nucleus, the locus coeruleus, in the floor of the fourth ventricle, travelling upwards in the brain stem, down into the lateral hypothalamus, looping back in the cingulum to give rise to terminals distributed to the entire cerebral cortex. Secondly, the ventral bundle of noradrenaline neurones, arising from cell body groups in the caudal brain stem, travelling up in the tegmentum, to be distributed mainly to hypothalamic areas.

All of these systems, therefore, send axons through the lateral hypothalamic area from which self-stimulation has generally been obtained. The question we ask is: which, if any, of these systems is involved in reward processes? The catecholamine hypothesis of self-stimulation clearly predicts that it should be possible to obtain self-stimulation with electrodes located within one of the cell bodies of origin of these systems. Our strategy, therefore, was to study self-stimulation at the level of the cell bodies of origin. Firstly, at this level here, including dopamine neurones. Secondly, through the cell bodies of origin of the dorsal bundle and then of the cell bodies of origin of the ventral bundle.

Firstly, therefore, we're studying a section through the midbrain to include the location of the dopamine neurones.

<**Crow over diagrams showing sections through the brain to show the function of dopamine neurones**>

Here we see the dopamine neurones across the ventral part of the midbrain. The cell bodies, fluorescing with the presence of dopamine, extend from the pars compacta of the substantia nigra, this has been labelled the A9 area, and the cell bodies here give rise to the terminals in the corpus striatum, across the midline to include the cell bodies of the A10 area, and these cells give rise to terminals in the nucleus accumbens and tuberculum olfactorium – an area referred to as the mesolimbic dopamine area. What we were interested to see, therefore, was whether at this level of the brain stem, self-stimulation sites correspond to the distribution of dopamine neurones.

This section shows that they do. Here we are looking at a cross-section through the brain stem at a level 4.5mm posterior to bregma. Each dot or circle here represents an electrode site tested for self-stimulation in one rat. Open circles representing those sites from which self-stimulation could be obtained and close circles those from which it could not. A band of positive sites extends across the ventral midbrain here, following closely the distribution of dopamine neurones and including also the interpeduncular nucleus. From this distribution alone one cannot conclude that it is activation of dopamine neurones that supports self-stimulation, but other experiments allow one to exclude other possibilities. For example, the fibres of the medial lemniscus pass here, rostrally, just dorsal to the dopamine cell bodies. One can exclude these as the substrate of self-stimulation by implanting electrodes further caudally along this pathway, and these electrodes do not support self-stimulation. Again, the fibres of the superior cerebellar peduncle decussate at this level here, and again, by a similar strategy one can exclude this pathway as the basis of the self-stimulation phenomenon.

00:10:21:00

<**Crow to camera, then over diagram showing a further cross-section of the brain**>

Another line of evidence is pharmacological. Drugs which inhibit the synthesis of both catecholamines, dopamine and noradrenaline, are good inhibitors of self-stimulation

responding. But drugs which inhibit the synthesis of noradrenaline alone are generally rather variable in their effects on self-stimulation. Therefore, we have quite a good case that activation of dopamine neurones supports self-stimulation responding.

The second major finding of this study was that there was a second group of positive sites in the midbrain and these are located considerably further dorsal to the band of sites in the ventral midbrain, here. In fact, these sites were quite close to the point at which the fibres of the dorsal bundle of noradrenaline neurones pass through the midbrain on their way into the lateral hypothalamus. Could it be that these electrode sites, here, support self-stimulation because they activate the fibres of the dorsal bundle? A simple prediction of this hypothesis is that it should be possible to obtain self-stimulation from the cell bodies of origin of the dorsal bundle, that is, in the nucleus locus coeruleus.

<**Crow over slide showing the cells of the locus coeruleus, then over diagrams of cross-sections through the brain stem at the point of the locus coeruleus**>

This slide shows the cells of the locus coeruleus, stained with a monoamine oxidase technique. Here, the line of the fourth ventricle separates the cerebellum above from the brain stem below. The cells of the locus coeruleus are located in the lateral part of the floor of the fourth ventricle. This nucleus is unique in the brain in consisting almost exclusively of noradrenaline-containing cell bodies and one can see here how closely localised they are to this site.

In a series of experiments, we implanted electrodes in the region of the locus coeruleus. Here we're looking at a cross-section through the brain stem, 8.5mm posterior to bregma. Each open circle again represents a site from which we could obtain self-stimulation. Here is the locus coeruleus in the lateral part of the floor of the fourth ventricle and one can see, whereas we have a number of negative sites in the cerebellar substance lateral, ventral and medial to the locus coeruleus, we have a number of positive sites located around or actually within the locus coeruleus itself. Again, at a slightly more posterior level, 9mm caudal to bregma, in other words

0.5mm posterior to the section we've just been looking at, we see the same distribution of positive sites directly around the locus coeruleus and negative sites further away.

Now, in each of these cases we have further evidence that these electrodes are actually activating the fibres of the noradrenergic system.

<**Crow over graph showing results of an experiment on electrically stimulated rats comparing levels of noradrenaline metabolite**>

In a series of rats, we studied the turnover of noradrenaline in the cerebral cortex, that is, in the terminals of distribution of this system, by looking at the noradrenaline metabolite hydroxymethoxyphenylglycol. We stimulated each rat under anaesthesia for an hour before killing the rats and removing the two cerebral cortices and measuring the levels of the noradrenaline metabolite.

In the series of rats which had self-stimulated, electrical stimulation caused a rise in the noradrenaline metabolite in the ipsilateral cortex, each electrode being implanted on the left side, but no rise in the contralateral cortex. By contrast, in a series of rats in which we did not obtain self-stimulation, stimulation did not, of course, arise of the noradrenaline metabolite.

<**Crow to camera, then over diagrams showing further cross-sections of brain tissue**>

From these experiments, it appeared that self-stimulation could be obtained not only by activation of dopamine neurones but also by activation of noradrenaline neurones from the locus coeruleus. One might reasonably ask whether each of the ascending catecholamine systems is a reward pathway. We tested this by implanting electrodes in the region of third bodies of origin of the ventral bundle in the caudal brain stem.

Here, we're 14mm caudal to bregma, and we implanted a series of about 30 electrodes in a coronal section including the A1 and A2 areas. We were able to

obtain 4 implantations in the region of the A2 area and about half a dozen close to the cell bodies of the A1 area, and none of these electrodes supported self-stimulation, nor were we able to obtain it with electrodes implanted on the ascending fibres. It appears, therefore, that this system does not support self-stimulation and is not, therefore, in this sense a reward pathway.

In conclusion, therefore, we have evidence that two of the three major ascending catecholamine-containing systems – the dopamine neurones arising from the ventral mesencephalon and the dorsal bundle of noradrenaline neurones arising from the locus coeruleus – function as reward pathways, but that the ventral bundle of noradrenaline neurones does not.

00:16:05:00

<**Crow to camera, then over film clip of rat with electrodes implanted in its brain, stimulating reward mechanism when it presses levers; firstly with electrodes in dopamine centres, then in the locus coeruleus. Then back to camera**>

Now, one of the most striking findings of these experiments was that the form of self-stimulation in the two cases was quite different. Let's look again at the film made in the Physiology Department at the University of Aberdeen.

With electrodes activating the dopamine neurones, such as one sees here, what one observes is quite a marked increase in locomotor activity and also sniffing and gnawing, searching behaviour. Someone described the stimulus in these cases as being like a goad without a goal, seems more like a promise of reward rather than the reward itself. It's perhaps not too anthropomorphic to say that the stimulus is exciting but not entirely satisfying. In terms of learning theory one might say it's drive inducing rather than drive reducing.

With an electrode in the locus coeruleus, the behaviour we see is quite different. In general, lever pressing is much more slowly established and once established is

accompanied by none of the excitation seen with the dopaminergic electrodes. Here, lever pressing behaviour follows a regular and stereotyped pattern.

Now, if you recall the two possible functions of reward I mentioned earlier, it appears that activation of the dopamine system corresponds much more closely to what one would expect from activation of an incentive motivational system – that is, of a system which energises and directs the animals' behaviour toward possible rewards in the environment. On the other hand, if one's looking for the role of reward in learning, perhaps the locus coeruleus, with its terminal distribution to the cerebral cortex, is a more promising candidate.

We have some evidence on these possibilities from lesioning experiments. Let's look first at the dopamine neurones.

<**Crow over diagram showing cross-section of brain with different responses of three main areas after suffering lesions**>

Here we know that bilateral lesions of this system lead to aphagia, adipsia and akinesia. Rats with such lesions have severe motor impairments and also motivational impairments. With unilateral lesions they show attentional deficits to the contralateral sensory field; these are perhaps the sort of defects one might expect from a system which was necessary for making approach responses to biologically significant stimuli.

Turning to the dorsal bundle, the position is less clear. Here there is some evidence that lesions, while causing no serious motor defects, do cause some impairment of the ability to adapt to a changing environment but the precise nature of the deficit is not yet clear.

In the case of the third system, the ventral bundle of noradrenaline neurones, lesions lead to increased food intake and weight gain. It has been suggested by Alskog and others that this system functions as a satiety mechanism and you will recollect that this is a system which does not support self-stimulation.

<**Crow to camera**>

Now, there is an interesting relationship between these pathways and the afferent pathways involved in the detection and ingestion of food. Olfaction and gustation are both chemoreceptor modalities whose primary function is to detect and select materials suitable for ingestion. The olfactory pathways appear to have an association with dopaminergic neurones insofar as there are neural pathways from the olfactory bulbs to the interpeduncular nucleus, which we've seen is closely related to the dopamine cell bodies.

The locus coeruleus, on the other hand, lies at the head of the visceral afferent column and a major contribution to this column is from the tractus solitarius which receives the primary endings of gustatory neurones.

It's possible, therefore, that there's a relationship between these two catecholamine systems which support self-stimulation and gustatory and olfactory pathways. Perhaps in the primitive organism, these systems of catecholamine neurones mediate the behavioural effects of rewarding gustatory and olfactory stimuli.

The origins of the third pathway, the ventral bundle, are quite closely related to two nuclei which receive ascending fibres from the viscera, including, presumably, the stomach.

It's possible, therefore, that each of these catecholamine systems is related to a major afferent pathway concerned with food intake.

00:21:19:00

Let's try to construct a general schema – this is bound to be speculative, but following Karl Popper, perhaps we needn't be too worried about this.

<**Crow over series of cartoon illustrations showing a hungry rat trying to reach and then eating a slice of cake**>

Consider a hungry rat beginning to look for food. As soon as he detects the smell of food, his behaviour changes. His motor activity increases and becomes directed toward the source of the stimulus. His behaviour is motivated to reducing the distance between him and the stimulus source. At this point, when he senses that he's not able to reach the food, we would expect his behaviour to be very much like that which we see in a rat with an electrode activating the dopamine neurons.

Now the most important stimulus in this situation, I think, is the olfactory one. Sight is no doubt important when he's learned by experience that the smooth white surface represents food, but olfaction, as a distance receptor of chemical detection, is of more fundamental importance. Therefore the fact that there are pathways between the olfactory bulbs and the dopamine neurones in the midbrain appears to be of particular significance.

When, as a result of a strategy of trial and error, the animal finally succeeds in its attempts to reach the food, the relevant modality is gustation. No longer is increased musculoskeletal exertion required; the appropriate reaction at this point, besides ingestion, is to record the particular strategy which finally succeeded in getting the rat to the primary reward. This, one might suppose, could be the function of the dorsal bundle of noradrenaline neurones. And the possible relationship of the locus coeruleus to the gustatory afferent mechanisms of the tractus solitarius is therefore of considerable interest.

Finally, all good things come to a satisfactory end. Perhaps, as a result of gastric distension and activation of ventral noradrenaline pathway, the behaviour is finally switched off. The satiety signal cuts out what, in these circumstances, might have turned into an excessive and damaging pursuit of positive reward.

<**Crow to camera**>

In this way we can see that perhaps the mechanisms of reward have developed out of a primitive need to detect food in the external environment at the point of entry to the body and in the internal environment, and of the necessity to mobilise an appropriate response. No doubt in the course of evolution these mechanisms have become more flexible and have come to serve much more varied behavioural ends.

Some 2000 years before Bentham, the philosopher Epicurus wrote that the beginning and route of all good is the pleasure of the stomach. Even wisdom and culture must be referred to this. Perhaps he was right.

<**End credits**>