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• *This new section carries reports on interesting recent developments in various areas of biology.*

How "carrots and sticks" are encoded in the brain: motivation, reward, addiction and fear

Motivation for specific tasks derives significantly from environmental feedback. For instance, if performance of an action results in immediate sensation of pain, I am likely to avoid repeating it; however, if the action results in pleasurable feedback, I will look for an opportunity to do it again. Thus, one learns through trial and error to perform actions that are positively reinforced and avoid those which result in negative reinforcement. The cognitive and even cellular bases for these psychological phenomena have begun to be unravelled by combining psychological studies with positron emission tomography (PET), functional magnetic resonance imaging (fMRI), electrophysiology, and biological chemistry.

Rats may be trained to repeat complex actions, such as traversing a maze or operating a lever, if the performance of this action results in a food reward. In 1954, Olds and Milner announced that the food reward could be effectively substituted by electrical stimulation of specific regions of the brain; in fact, the rats would learn to stimulate themselves. In ensuing years, the basal forebrain as well as some other brain regions have been identified not only as part of a brain-stimulation reward pathway, but also as the pathway activated by natural reward.

The natural reward system involves many regions of the brain and many neurotransmitter systems. However, a substantial role is played by the dopaminergic mesocorticolimbic pathway which impinges on the basal forebrain. More simply put, neurons that secrete or respond to the transmitter dopamine, play a very important role in the sensation of reward, which critically underlies the reinforcement of particular behaviours. Food, success, and sex activate dopaminergic transmission in the basal forebrain and behaviours directed towards these commodities are normally reinforced in the brain. Thus, healthy animals (those selected for in the wild) are motivated to achieve social and sexual success. A subset of animals in any species, for instance rogue lions and chimpanzees among non-human animals, or saints, scholars, and cocaine addicts in human society, do not play by the same rules as others. Behaviours that stimulate their reward pathways are presumably different in some way. This has been demonstrated recently by fMRI scanning studies on cocaine addicts where brain activities were measured *in vivo* during the anticipation, rush, high, and low phases that occur at different stages of cocaine reception (Breiter *et al* 1997). Cocaine, which blocks the re-uptake of dopamine following its release, prolongs dopaminergic transmission in parts of the brain that constitute the reward pathway. Thus, by directly activating an acute sensation of reward, cocaine seeking behaviour is very strongly reinforced. It is probably not a coincidence that it is those with fewer rewards from "normal life" that are more frequently attracted to an easy pharmacological solution. The sensitivity of the reward pathway to different environments is also influenced by genetic rather than epigenetic phenomena (Rocha *et al* 1998).

Like all mammalian systems, the brain shows a remarkable tendency towards homeostasis. For this reason, chronic use of cocaine probably results in adaptation of the reward system, such that the "set point" for hedonism (intense sensation of reward) is altered. The reduced sensitivity of this adapted reward system may now increase craving for cocaine stimulation (for a more rigorous and detailed review read Koob and Moal 1997). While reward-seeking is a major source of motivation, fear, the desire to avoid negative reinforcement in the form of pain, is also a strong source of motivation. Like the sensation of reward, fear may be induced in rats by direct electrical stimulation of a specific anatomical region of the brain—the central nucleus of the amygdala.

In classical conditioning experiments, a conditioned stimulus such as a high pitched tone can be associated with a negative (unconditioned) stimulus such as electric shocks applied to the feet of a rat (footshock). Recent studies have shown that while a tone produces only a small response in the amygdala of an untrained rat, it produces a greatly enhanced response in the amygdalar

neurons of a rat conditioned to associate this tone with footshocks. Thus, the neuronal basis of fear conditioning has begun to be unravelled (McKernan and Shinnick-Gallagher 1998; Rogan *et al* 1998).

While a tone-footshock association may be made following a single pairing of the two stimuli, for the same tone to be associated with a reward, such as a food reward, several pairings of the two stimuli are usually required. Thus, fear-based associations are learned faster than reward-based associations. When one considers the evolution of mammals, it is easily apparent why brains may function in this manner. The apparent efficiency of fear-based training compared to the reward-based method may superficially suggest alterations to the now-fashionable, politically-correct approach to rearing children or students. Perhaps the traditionalists had it right: "spare the rod and spoil the child". However, fear-based learning, while efficient, is extremely limited. The emotion of fear appears so strong that, in the fearful state, new associations are actively blocked. This blocking may occur via the secretion of opiates by amygdalar neurons which prevent the formation of new associations (reviewed by Fanselow 1998). In evolutionary terms, our brains may have evolved to ensure that fear (such as that generated by the sight of a hungry tiger) causes us to ignore all non-fearful stimuli until the source of fear is gone. Thus, fear-based training programs, while efficient, probably have a price that should greatly restrict their general use.

References

Breiter H C, Gollub R L, Weisskoff R M, Kennedy D N, Makris N, Berke J D, Goodman J M, Kantor H L, Gastfriend D R, Riorden J P, Mathew R T, Rosen B R and Hyman S E 1997 Acute effects of cocaine on human brain activity and emotion; *Neuron* **19** 591–611

Fanselow M S 1998 Pavlovian conditioning, negative feedback, and blocking: mechanisms that regulate association formation; *Neuron* **20** 625–627

Koob G F and Moal M L 1997 Drug abuse: hedonic homeostatic dysregulation; *Science* **278** 52–58

McKernan M G and Shinnick-Gallagher P 1998 Fear conditioning induces a lasting potentiation of synaptic currents *in vitro*; *Nature (London)* **390** 604–607

Rocha B A, Scearce-Levie K, Lucas J J, Hiroi N, Castanon N, Crabe J C, Nestler E and Hen R 1998 Increased vulnerability to cocaine in mice lacking the serotonin 1-B receptor; *Nature (London)* **393** 175–178

Rogan M T, Staubli U V and LeDoux J E 1998 Fear conditioning induces associative long-term potentiation in the amygdala; *Nature (London)* **390** 604–607

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CpG-containing oligodeoxynucleotides as new generation adjuvants in DNA and protein vaccines

Since ages, Freund's Complete Adjuvant (FCA) has been used by immunologists to boost the immune response in experimental animals. Due to inflammatory side effects however, use of FCA is not permitted in humans and search is on for a better adjuvant. Recently several reports have shown that bacterial DNA acts as potent adjuvant, promoting a T-helper 1 (Th1) immune response. An immune response can be classified as a Th1 type characterized by the generation of cytokines like interferon gamma (IFN-γ) and interleukin-2 (IL-2), or a Th2 type in which cytokines like IL-4, IL-5, IL-10 and IL-13 are produced. Th1 cytokines influence the immune response and push it towards the generation of cell mediated immune (CMI) responses like cytotoxic T cells (CTL)