DOPAMINE AND ADDICTION:
THE MEDIUM IS THE MESSAGE

Paul Cumming

A large variety of addictive substances and behaviors has been linked to changes in brain dopamine neurons, which are connected to pathways intimately involved in motivation and reward. Indeed, it has been claimed that all addictions, including nicotine, amphetamine, cocaine, alcohol, and perhaps gambling converge on dopamine mechanisms in parts of the brain subserving reward or reinforcement. However, physiological studies suggest that this simple model may confuse the message (mediated by dopamine) that a reward has taken place, with the reward itself. Dopamine may in fact subserve the education of the brain to anticipate strategies for obtaining rewards in the future, but some drugs may hi-jack this normal motivational and adaptive process and become an end in themselves. Many addictive drugs produce short term changes in receptors for dopamine and other neurotransmitters. While these temporary changes may account for the unpleasant aspects of the acute phase of withdrawal, other factors must underlie craving and the risk of relapse in drug addiction. It is coming to be understood that these long term changes are mediated by intracellular proteins under the control of dopamine receptors, which ultimately serve to alter gene expression, thus inducing long-lasting changes in neuronal activity. While many biochemical studies of addiction have been carried out in experimental animals, the advent of positron emission tomography (PET) has made possible the investigation of dopamine systems in living humans. Short term and chronic changes in brain dopamine have been noted in PET studies of nicotine, cocaine, alcohol and amphetamine addicts. It is hoped that a more complete biochemical understanding of the nature of addiction will ultimately lead to improved treatments.

»Addiction, like nostalgia in general, is a form of mourning, an attempt to keep the vanished love object close at hand…. And, like other forms of mourning, addiction keeps count.«

ANN MARLOWE, *HOW TO STOP TIME*

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An understanding of the relationship between brain dopamine and addiction has become well-established among the general public; It has been claimed in the popular press that one quarter of the adult population suffer from an obscure reward deficiency syndrome related to an inadequate dopamine system. The assumption is that this deficiency syndrome is symptomatically alleviated by self-medication with a broad pharmacopoeia, including tobacco, alcohol, heroin, and by drug surrogates such as chocolate, jogging, shopping, or gambling. The implication is that brain dopamine is the route to all pleasures and the route to all vices. In an extreme form of this model, it has been assumed that the release of dopamine in the brain is synonymous with or identical to the reward itself. In other words, people are addicted to dopamine, and the diverse means for bringing about an increase in dopamine release in brain are simply different means to the same end. This notion seems reminiscent of the famous assertion of the Canadian media theorist Marshall McLuhan (1911-1980) that »the medium is the message«, by which he meant that the technical means of communication is somehow identical with the actual message. But what is dopamine, and what message does it normally transmit to the brain?

Dopamine is a small molecule derived from the essential amino acid tyrosine. In the blood, dopamine serves as a hormone regulating cardiovascular tone, and it is the precursor for the adrenal hormones noradrenaline and adrenaline, which instruct the body to be prepared for »fight or flight«, by increasing cardiac output, and mobilizing sugar stored in the liver. But dopamine present in the blood cannot enter the brain. The production of dopamine in brain occurs within specific groups of brain cells (neurons) possessing the enzymes for synthesizing dopamine, storing it in synaptic vesicles and releasing the stored dopamine in a controlled manner. A large proportion of these dopamine cells is located in a region of the brain known as the mesencephalon, meaning the mid-brain. In post mortem specimens, the location of the dopamine cells can be discerned as a pair of black patches (the *substantia nigra* to early anatomists) the size of a small fingernail. The black color is due to the presence of neuromelanin, a byproduct of dopamine synthesis closely related to the skin pigment melanin. In the 1950s and 1960s it was determined that the mesencephalic dopamine cells, numbering less than 500,000, give rise to fibers ascending to anterior parts of the brain, especially to a structure lying beneath the frontal cortex, known as the extended striatum.

The human striatum, which is the size and shape of two side-by-side quail eggs, is composed of subdivisions known as the putamen, the caudate, and the nucleus accumbens. Each of these three divisions contains other brain cells that are endowed with dopamine receptors, making them responsive to dopamine released in their vicinity. The three anatomical divisions of the striatum all receive similar dopamine inputs, but are distinguished by the parts of cerebral cortex with which they are integrated or connected. Specifi-

cally, the putamen is linked to the motor and sensory cortex, the caudate is linked to parts of the cortex involved in cognition and sensory integration, while the nucleus accumbens is most linked to the limbic cortex, which is involved in motivation. So, dopamine cannot be said to have a single unitary function. Rather, dopamine does *something* that depends on the type of cerebral cortex involved.

What then is it that dopamine does, once released in the striatum? It is now understood that dopamine communicates with striatal neurons via several types of dopamine receptors. Activation by dopamine alters the electrical activity of those striatal neurons bearing dopamine receptors. These cells in turn project to other neurons ultimately feeding back to the cerebral cortex, which, itself innervates the striatum. As such, dopamine is just one player in a loop-like circuit of neurons, the purpose of which seems to be to modulate its own activity in a controlled manner, imparting a sort of plasticity allowing the brain to learn or adapt to new circumstances. However the role of dopamine in brain function was first understood by exclusion, by observing what happens in the absence of dopamine. The loss of melanin-pigmented dopamine neurons in brain of patients dying with Parkinson's disease was described in the 1950s, leading in the 1960s to the rationale use of levodopa for the alleviation of disease symptoms. A notable symptom of Parkinson's disease is rigidity of the skeletal muscles, suggesting that dopamine is a facilitator of normal movement. More properly, it might be said that dopamine mediates the correct response to sensory feed-back from the muscles and tendons such that movement is achieved by modulation of a baseline muscle tone.

Modern imaging studies with positron emission tomography (PET) indicate that the dopamine deficiency of Parkinson's disease is greatest in the putamen, which is linked to the motor and sensory pathways.

In the very early 1970s, it was discovered that rats were motivated to receive pulses of electrical stimulation via an electrode directed towards the dopamine fibers ascending en route to the striatum (Breese et al., 1971). Rats could be trained to press a lever hundreds of times for a single pulse of electricity, and, famously, would continue pressing a lever for electrical »reward« to the exclusion of all other activities. Around the same time it was noted that rats would continue to press a lever for small intravenous injections of cocaine, only so long as the dopamine innervation of the nucleus accumbens was intact (Roberts et al., 1977). While the behavioral stimulant effect of cocaine is unaffected by lesions to the nucleus accumbens, the motivation to take cocaine is gone; the salt has lost its savor. Together, these findings in rats helped provide the basis for the linkage between dopamine release in the nucleus accumbens of the ventral striatum and the rewarding and motivational aspects of stimulant drugs, as distinct from their behavioral effects, which are mediated by the motor systems of the dorsal striatum.

During the early 1980s, the cerebral microdialysis technique became available for studies of dopamine release evoked by psychostimulant drugs. In this technique, the extracellular milieu is sampled through a small porous plastic fiber, and the concentration of dopamine and its metabolites in the fluid of the brain can be measured during treatment with psychoactive compounds. The preferential release of dopamine in the rat nucleus accumbens by amphetamine was an early finding using this technique (Hernandez et al., 1987). The list of drugs with abuse potential for humans and which increase dopamine release in the nucleus accumbens of rats now includes nicotine, amphetamine, cocaine, and ethanol (di Chiara and Imperato, 1988). Natural reinforcers such as food likewise evoke a dopamine release in the rat nucleus accumbens. Thus, there seemed to be a clear association between dopamine release, obtained by any number of means, and the experience of positive motivation, commonly known as reward. In a simple interpretation of this finding, dopamine release came to be identified with the reward itself (the medium is the message). However, this identification failed to clarify the nature of addiction, since it did not explain why certain drugs, with repeated use, establish themselves as primary motivators, whereas food intake, for example, is maintained within reasonable limits for most of us. Starving people may commit crimes to obtain food, but well-fed people seldom commit crimes to satisfy a craving for sugar.

The biochemical factors underlying addiction are only now coming to be understood. In the first instance, pharmacologists consider that addiction is based upon a form of habituation, where the nervous system has become accustomed to an excess of some pharmaceutical. The physiological manifestations of this process have been linked to changes in neuroreceptors. Hence, repeated exposure to nicotine results in inactivation of nicotinic receptors in brain of experimental animals (Ochoa et al., 1990), chronic morphine treatment decreases the abundance of opioid receptors (Turchan et al., 1999) and chronic methamphetamine treatment decreases the abundance of dopamine receptors (McCabe et al. 1987), which are indirectly activated by amphetamine-evoked dopamine release. These and other neurotransmitter systems interact in complex manners; Thus, repeated nicotine treatment inactivates dopamine receptors in rodent brain (Janson et al., 1992), an effect presumably mediated by the ability of nicotine to activate dopamine release above normal levels. These sorts of changes doubtless contribute to the phenomenon of tolerance, whereby habitual drugs users can consume quantities which might be fatal to inexperienced users. Furthermore, sudden cessation of the drug of choice leaves the brain and peripheral tissues bereft of adequate activation of these receptors, which results in the acute syndrome of withdrawal. It is this withdrawal which the drug user seeks to avoid; Withdrawal from opiates can evoke criminal or reckless behavior on the part of the unfortunate addict.

However, it is far from certain that the changes in receptor density noted above are irreversible. For example, withdrawal from methamphetamine during several weeks resulted in normalization of the dopamine markers in brain of rats which had become accustomed to self-administer the drug (Stefanski et al., 2002). Nonetheless, craving and the risk of relapse can persist for many years in abstinent drug users. Additional factors, down-stream to the receptors themselves must account for the persistent risk of relapse. In order to understand the long-term consequences of drug addiction, it must be considered that dopamine receptors are merely switches for informing a cell bearing the receptors that a signal has arrived. When dopamine, for example, binds to its receptors in brain, its signal is transferred to the cell bearing those receptors by specific proteins which become activated by the binding of dopamine. In many neuroreceptors, the binding of the natural transmitter initiates a chain of events freeing into the cellular milieu a class of proteins characterized by their ability to bind the nucleotide GTP, a small molecule related to a basic chemical component of DNA. These proteins are collectively known as GTP-binding proteins, more frequently referred to as G-proteins. When released into the cell, the G-proteins in turn alter the activity of specific enzymes, which can influence the rate of generation of another small molecule, known as cyclic-AMP, which in turn binds to still other enzymes, altering their activities. Thus, if dopamine is the first messenger, the G-proteins liberated by activated dopamine receptors are known as second messengers. They activate a process known as a »signal transduction cascade«, in which many diverse molecular targets can be activated or inactivated, all under the regulation of dopamine receptors. Sometimes multiple neuroreceptor types converge on the same second messenger systems, such that the full complexity of the possible outcomes of receptor activation can be very complex indeed.

Activation of neuroreceptors by their neurotransmitters is necessary but not sufficient to initiate signaling within the cells bearing the receptors. Any process interfering in the abundance of the G-proteins, or their ability to interact with their preferred receptors, can alter the signaling in brain. Chemical destruction of G-proteins attenuates the reinforcing properties of both cocaine and heroin (Self et al., 1994), indicating that these two very different classes of drugs converge on common second messenger systems. Chronic exposure to morphine alters the properties of G-proteins in the noradrenaline-rich part of the brain of rats (Nestler et al., 1989), such that the responsiveness of these neurons is fundamentally altered. Part of the syndrome of opiate withdrawal, especially the anxiety, may be related to misregulation of the noradrenaline neurons via this mechanism. However, in order to elucidate the biochemical changes underlying long-lasting risk for relapse behavior, one must probe deeper still, and consider the way in which paths can be burned into the nervous system. Here we invoke what

has been called the terniary messengers, i.e. the proteins which are responsive to modulation by the secondary messenger.

If neurotransmitters such as dopamine modulate the G-proteins, which in turn regulate the activity of enzymes generating cyclic-AMP, what are the subsequent steps in signal transduction? Fifteen years ago it came to be appreciated that cyclic-AMP exerts a powerful regulation of other enzymes, known as protein-kinases, which serve to transfer a phosphate chemical group, very close in nature to the phosphoric acid which is so detrimental to the dental health of Coca-Cola addicts. The targets of the protein-kinase reaction are other proteins, collectively known as phosphoproteins. Proteins in general are large molecules, often containing hundreds of the amino acid building blocks. But incorporation of a single phosphate group into a phosphoprotein can fundamentally alter its properties, resulting in a profound alteration of the life of the cell. Therefore it is a matter of great interest that morphine acts by inducing, via cyclic-AMP-regulated enzymes, the tagging of intracellular proteins by phosphate (Guitart and Nestler, 1989). Among the diverse proteins modulated by these pathways is known as the cyclic-AMP response element binding protein (CREB), which has been implicated in the propensity to consume excessive amounts of alcohol (Pandey et al., 2004). CREB belongs to the family of transcription factors, which ultimately serve to signal the original neurotransmitter message to the cell nucleus, wherein the DNA, containing the entire genetic code resides. CREB and other transcription factors bind to DNA in such as way as to alter the expression of specific genes, which in turn can produce structural and physiological changes in the cell. CREB and other transcription factors can be modulated by cocaine (BT Hope, 1998), and nicotine (Pluzarev and Pandey, 2004); It is precisely this level of altered cellular behavior which is now thought to underlie the long lasting detrimental effects of addictive drugs. By changing gene expression, amphetamine, morphine and other addictive drugs may teach the brain a lesson it cannot forget, to the detriment of the owner of the brain in question.

Positron emission tomography (PET) is a relatively new tool for investigating the status of neurotransmitter systems in brain of living humans and experimental animals. Radiopharmaceuticals for PET are prepared on-site using a particle accelerator known as a cyclotron, a requirement imposed by the very short half-life (2-120 minutes) of the isotopes for PET studies. Upon injection of the radiopharmaceutical into the patient's blood, usually via an arm vein, it passes into the brain, and may accumulate in specific brain regions richly endowed with binding sites for the radiopharmaceutical in question. There, the radioactive atom ultimately decays, releasing a positron, which is the name for an anti-matter partner of an ordinary electron. After traveling some millimeters in the medium of the brain, the positron meets an electron head-on, and the two particles annihilate each other, releasing their entire energy ($E=mc^2$, in the famous formulation of Einstein) as two

very high energy photons known as gamma-rays. The two gamma-rays fly away from each other at the speed of light, but may encounter gamma-detectors, if the annihilation took place while the patient's head was inside a PET scanner. If the PET, which actually consists of rings of many hundreds of small detectors, counts two events, that is the arrival of two gamma-rays, simultaneously in the interval of one millionth of a second, it is registered that a radioactive decay had taken place at a point half-way between the two detector elements. Counting many million of these events, in conjunction with high-speed computers, allows the calculation of a picture or map, showing the distribution of radioactivity in the head as a function of time.

Unfortunately, PET has not yet proven useful for the study of second messenger systems or transcription factors, but has been mainly used for the study of changes in the number of neuroreceptors associated with drug addiction. In recent decades, PET has provided considerable evidence that dopamine is a key player in the unconditioned properties of many drugs with abuse potential. Dopamine receptors in human brain can be visualized and quantified in PET studies employing a radioactive drug such as [^{11}C]-raclopride, which binds to specific dopamine receptors in brain. Using this method, the abundance of dopamine receptors has been shown to be reduced in brain of living alcoholics (Volkow et al., 1996), and in patients suffering from cocaine dependence (Martinez et al., 2004). These findings are generally consistent that a wide array of addiction disorders are associated with changes in the availability of dopamine receptors.

The number of available dopamine receptors that can be detected during a particular PET scanning session is reduced by simple competition from brain dopamine for binding to the same sites. Consequently, pharmacological challenges or cognitive tasks altering dopamine release alter the PET signal. In [^{11}C]-raclopride-PET studies, smoking evokes a decline in [^{11}C]-raclopride binding, indicative of dopamine release of comparable magnitude to that evoked by amphetamine (Brody et al., 2004), cocaine, and other psychostimulants. Furthermore, the magnitude of the change in PET signal in the nucleus accumbens evoked by smoking correlates positively with the hedonic value experienced by individual smokers (Barrett et al., 2004). These findings with smoking, and comparable PET studies with cocaine and amphetamine, lend further support to the linkage between dopamine and rewarding properties of drugs of abuse. In some PET studies, natural reinforcers such as palatable food, have been also shown to evoked dopamine release in the nucleus accumbens, but the magnitude of the changes is generally less than that evoked by addictive drugs (Small et al., 2003). However, it is notable that the individual magnitude of these effects is greater in the pathologically obese (Wang et al., 2002), suggesting that the conditioned properties of palatable food may be greater in those with eating disorders, either due to a pre-existing condition, or reflecting a kind of over-learned association between food and reward.

A very high dose of nicotine is required to evoke a discernible decline in [^{11}C]-raclopride binding in striatum of living anesthetized pigs (Cumming et al., 2003), although smoking a single cigarette was sufficient to evoke a substantial decline in [^{11}C]raclopride binding in the human PET studies cited above. Thus, the effects of smoking on [^{11}C]-raclopride binding must be mediated by additional factors such as conditioning or expectation, or alternately by the complex pharmacology of tobacco smoke. The former possibility, that of cognitive modulation of the response to stimulant drugs, is supported by other PET studies in which an inert placebo could evoke an »amphetamine-like« decline in [^{11}C]-raclopride binding (de la Fuente-Fernandez et al., 2002). It is the experience of many drug addicts that exposure to an environment formerly associated with drug taking, is the most powerful evoker of craving. Ask any reformed smoker in a smoky bar! Recent pharmacological studies lend further support to this obvious relationship between environmental craving and environmental cues. In some sense, the cues evoke a memory of the addict's condition just prior to their last use of their drug. The nervous system remembers well what to do next, accounting for the great risk of relapse among addicts.

The lack of simple correspondence between PET results and conventional pharmacology, especially perhaps in the case of tobacco addiction, makes impossible the equating of dopamine and reward. Indeed, current thinking about the nature of tobacco addiction entails complex arguments about conditioned aspects of smoking behavior, in conjunction with sensitization of smoking-evoked dopamine release, such that the behavior eventually becomes self-supporting, irrespective of its primary rewarding properties (Balfour, 2004).

Dopamine in the motor striatum allows the correct modulation of muscle tone required for voluntary movement; its absence underlies the motor symptoms of Parkinson's disease. What analogous process could dopamine mediate in the nucleus accumbens, which differs from the motor striatum mainly with respect to its connectivity with limbic or emotion-related regions of the brain rather than the parts of the cerebral cortex which control the skeletal muscles? The simple relationship between dopamine in the nucleus accumbens and the experience of reward has been challenged on the basis of key experiments in awake, non-human primates. Researchers have recorded the electrical activity of dopamine cells projecting to the nucleus accumbens of monkeys performing behavioral tasks. Specifically, the monkeys were trained to associate a tone of sound with a squirt of fruit juice, which they find very rewarding. If dopamine release were synonymous with reward, the dopamine cells should have been active immediately following the juice administration. However, this was not the case. Instead, the electrical activity of the monkey dopamine neurons projecting to the nucleus accumbens increased only when an unexpected reward took place, not preceded by the usual musical tone (Schultz et al., 1977).

The findings of Schultz et al. could be interpreted to mean that dopamine activity in the nucleus accumbens informs the rest of the brain that a surprise reward has taken place, such that adaptive learning can occur so as to increase the likelihood of these rewards occurring in the future. In other words, dopamine instructs the nucleus accumbens to take note of what the rest of the brain was doing at the time of an unexpected reward, allowing for optimization of the attainment of future rewards. In the context of the motor system, dopamine may likewise inform the brain that there has been a disagreement between the command sent to the skeletal muscles and the consequent motor response. In Parkinson's disease, this optimization can no longer take place, resulting in rigid paralysis. In an extension of the Schultz model of dopamine and reward, addiction has been described as a »non- compensatable change in a temporal-difference reinforcement learning« algorithm (AD Redish, 2004). Here, cocaine, amphetamine, nicotine and other addictive substances hijack the mechanism for adjusting behavior in response to unexpected natural rewards, and focuses our learning and adaptive mechanisms on the behavior just preceding the non-compensatable stimulus, i.e. smoking or other drug-taking.

The truth about addiction must be related to the nature of the salience of natural rewards. We are not wired in a simple manner such that a decision to act or the evaluation of the consequences of our actions is based upon an accumulation of poker chips, or »reward units«. Rather, the poker chips, which may be measured in the units of dopamine release, convey the element of surprise when one experiences an unexpected reward. Addictive drugs erode normal motivational state by supplanting the message by the medium, which is the physiological mechanism for announcing that a reward has taken place. This conception will require a radical rethinking of the relationship between dopamine and addiction, and may serve to explain why associative factors such as cueing to environmental stimuli are key factors in evoking relapse for drug-taking; a smoky bar is the worst environment for a reformed smoker or alcoholic. Sigmund Freud, who attempted to treat morphine addiction with cocaine, famously discovered the failure of dopamine-activating drugs for the treatment of addiction. Future therapies will be designed to break the association between dopamine release and conditioned reward, which is the hallmark of addiction.

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