

What neurobiology cannot tell us about addiction

Harold Kalant^{1,2}

Department of Pharmacology, University of Toronto, Toronto, Canada¹ and Centre for Addiction and Mental Health, Toronto, Canada²

ABSTRACT

Molecular neurobiological studies have yielded enormous amounts of valuable information about neuronal response mechanisms and their adaptive changes. However, in relation to addiction this information is of limited value because almost every cell function appears to be involved. Thus it tells us only that neurons adapt to 'addictive drugs' as they do to all sorts of other functional disturbances. This information may be of limited help in the development of potential auxiliary agents for treatment of addiction. However, a reductionist approach which attempts to analyse addiction at ever finer levels of structure and function, is inherently incapable of explaining what causes these mechanisms to be brought into play in some cases and not in others, or by self-administration of a drug but not by passive exposure. There is abundant evidence that psychological, social, economic and specific situational factors play important roles in initiating addiction, in addition to genetic and other biological factors. Therefore, if we hope to be able to make predictions at any but a statistical level, or to develop effective means of prevention, it is necessary to devise appropriate integrative approaches to the study of addiction, rather than pursue an ever-finer reductive approach which leads steadily farther away from the complex interaction of drug, user, environment and specific situations that characterizes the problem in humans.

Keywords Addiction, molecular genetics, neuroadaptation, neuronal response mechanisms, research strategy, reductionism vs. integration.

Correspondence to: Harold Kalant, Department of Pharmacology, Medical Sciences Building, 1 King's College Circle, University of Toronto, Toronto, Canada M5S 1A8. E-mail: harold.kalant@utoronto.ca

Submitted 1 July 2009; initial review completed 15 July 2009; final version accepted 15 July 2009

WHAT IS ADDICTION?

It may seem unnecessary to begin a paper in *Addiction* with a question about the meaning of addiction. However, the reason for so doing will become clear shortly. Although the World Health Organization (WHO) Expert Committee recommended many years ago that the term 'addiction' be replaced by the term 'dependence' [1], both terms have continued in use and have generally become accepted as synonymous.

The DSM-IV-TR definition of dependence includes only one fundamental element: compulsive use of the drug despite the occurrence of adverse consequences [2]. However, a more detailed description of the 'dependence syndrome' includes both physical components (increased tolerance to the drug; repeated experience of withdrawal symptoms; use of the drug to prevent or relieve withdrawal symptoms) and behavioural signs of loss of control over drug use (e.g. increasing prominence of drug-seeking behaviour, even at the cost of disruption of other important parts of the user's daily life; use of larger amounts

than intended; inability to cut down the amount used, despite persistent desire to do so; and awareness by the user of frequent craving). Other definitions by various expert bodies have generally been similar in content.

An *ad hoc* committee set up by the Royal Society of Canada to review the evidence concerning tobacco/nicotine [3] concluded that the only elements common to all definitions of addiction are a strongly established pattern of repeated self-administration of a drug in doses that produce reinforcing psychoactive effects reliably, and great difficulty in achieving voluntary long-term cessation of such use, even when the user is strongly motivated to stop.

The emphasis here is on the word 'self-administration'. Physical dependence can be produced by large doses of an opioid analgesic administered therapeutically by a health care professional to a patient with severe pain, yet such patients rarely become compulsive drug-seekers. The situation was different for wounded veterans of the American Civil War, who were issued syringes and morphine tablets for self-administration;

many of them did indeed become victims of what was later known as ‘soldier’s disease’ [4]. In other words, addiction is not produced by a drug, but by self-administration of a drug; the difference is of fundamental importance. There are, of course, other important differences between the two groups. The Civil War veterans’ self-administration of morphine was socially approved, and they were provided with the means of carrying it out. In contrast, the administration of morphine on a doctor’s prescription to patients for relief of pain is also socially approved, but the patients would be socially disapproved of if they sought to obtain and self-administer illicit opioid for other purposes. Nevertheless, in either case it is the self-administration that underlies the definition of addiction or dependence.

It is regrettable, therefore, that one still finds in the experimental literature many studies carried out with the most sophisticated modern techniques, but with the basic flaw that animals are presumed to have been rendered ‘addicted’ by continuous exposure to alcohol vapour in a closed chamber, or by repeated intraperitoneal or intravenous injection of an opioid, or cocaine, or some other presumably ‘addictive drug’. Such experiments may yield important information about biological mechanisms of tolerance or physical dependence, but these are not the same as addiction [5,6].

NEUROBIOLOGICAL RESEARCH ON ADDICTION

Leaving aside such flawed studies, what can we hope to learn about ‘real’ addiction from research on the interaction of drugs with the whole spectrum of phenomena that constitute the field of neurobiology. The past two decades have seen dramatic and rapid progress in the field of neurobiology, resulting from the application of a dazzling array of new techniques ranging from *in vitro* molecular methods to brain imaging procedures in intact, conscious subjects performing a variety of behavioural tasks. It would be impossible to cover here the whole range of new knowledge arising from such work, and conclusions will therefore be drawn from a brief look at four of the major areas in which these modern methods have been applied to the study of addiction. These are (i) drug actions on intracellular signalling systems which mediate cell responses, (ii) synaptic plasticity in the course of chronic drug exposure, (iii) the role of dopaminergic and other constituents of the so-called ‘reward system’ and its various modulators in the brain and (iv) the role of genetic factors in addiction.

INTRACELLULAR SIGNALLING SYSTEMS

All living cells, and especially nerve cells, have an innate ability to adapt to changes produced by influences exter-

nal to them, and the adaptations are usually in the direction opposite to the changes that initiated them, thus tending to restore the previously existing equilibrium. For example, a touch sensor in the skin discharges nerve impulses at a low constant frequency when it is at rest. Application of a touch stimulus to that sensor causes it to fire a burst of impulses at a much higher frequency that is proportional to the pressure of the applied touch. If the stimulus is maintained with the same pressure, the sensor gradually adapts by reducing its sensitivity and the firing frequency gradually falls back to the resting rate. If the touch stimulus is then suddenly removed, the adaptive change is unopposed and the firing frequency of the cell suddenly drops much below the resting level, constituting a sort of ‘stimulus withdrawal reaction’. Finally, in the continued absence of the stimulus, the sensor gradually loses the adaptive change and returns to its resting firing rate [7]. Similarly, when neuronal functions are disturbed by the actions of drugs, adaptive changes occur that are usually opposite to those induced by the initial action of the drug, and thus tend to overcome the drug effect, producing an ‘acute tolerance’ [8,9]. If the drug is then removed suddenly, as by the application of a receptor blocker, the adaptive changes are unmasked and become the basis of an acute withdrawal reaction [10–12].

The understanding of these drug-induced adaptive changes has been facilitated by the great advances made in detailed knowledge of the so-called ‘signalling cascades’, the chains of molecular events initiated by the binding of neurotransmitters to their receptors on the surface of a neurone and ending in a response by the cell. The actions of a variety of potentially addictive drugs on these chains of events have been studied, both after single administration and after repeated administration of the drug.

In the case of morphine or other mu-opioid receptor agonists, for example, combination of the opioid with its receptor activates a G-protein attached to the receptor, which in turn affects a variety of enzymes and other proteins in the cell membrane or within the cell [13]. *Inter alia*, it inhibits adenylate cyclase and also inhibits ion channels in the cell membrane that maintain the excitability of the cell, so that the cell becomes less responsive to stimuli and releases less neurotransmitter at its presynaptic terminals. In contrast, it activates several different protein kinases that phosphorylate specific proteins, and the phosphorylated proteins produce adaptive functional changes that tend to offset the effects of the opioid on the cell. These functional changes include alterations in various cell membrane receptors, ion channels and enzymes, as well as intracellular alterations in energy metabolism, ion movements and activation of various genes that direct the synthesis of specific protein con-

stituents of the cell, in acute as well as chronic drug exposure [14,15]. When the opioid drug is withdrawn, these adaptive changes become the basis of a withdrawal reaction.

Similar types of cellular changes are produced acutely by the exposure of neurones to cocaine, to cannabis and to other drugs of dependence, depending upon what types of drug receptor are found on an individual neurone. Even ethanol, although it does not have specific receptors on the cell surface analogous to those for opioids, cocaine or cannabinoids, binds to numerous cell membrane and intracellular proteins, including other receptors, enzymes and ion channels [16–19]. Not surprisingly, therefore, chronic exposure to any of these drugs results in corresponding increases or decreases in adenylate cyclase, cyclic adenosine monophosphate (cAMP), mitogen-activated protein kinase (MAPK), extracellular regulated kinase (ERK), cFos and the other components of the cell's internal signalling mechanisms [20,21].

However, similar increases or decreases in these signalling molecules are found in nerve cells that are exposed to stimuli of other kinds than drugs, for example stressors, or sensory stimuli involved in learning, or that evoke memory, and so forth [22–26]. What this tells us, therefore, is that these signalling pathways are parts of the cell's basic machinery for responding to a wide variety of functional disturbances of different kinds [25]. Obviously they will be called upon whenever the cell's equilibrium is disturbed by a stimulus, whether drug-induced or other. When a cell is activated, it responds by using the machinery with which it is endowed. The adaptive changes in the cell's messenger systems are *mechanisms* of cellular adaptive responses, including tolerance and physical dependence, but also including sensory adaptation, learning and other purely behavioural phenomena. A mechanism is not the same as a *cause*. In this context, the cause is that which calls the mechanism into action and directs it toward the relevant and appropriate response.

SYNAPTIC PLASTICITY

Adaptive responses to various types of functional alteration are displayed not only within single neurones but also at synapses between neurones [14,27]. The synaptic adaptive responses that have been studied most intensively are long-term potentiation (LTP) and long-term depression (LTD). As the names imply, LTP is a process of long-lasting facilitation of impulse transmission from one neurone to another when the synapse between them is used repeatedly under certain conditions. Conversely, LTD is a long-lasting decrease in impulse transmission. LTP and LTD may be produced by both pre- and postsyn-

aptic processes. Among the postsynaptic mechanisms is a change in the ratio of two types of glutamate receptor, the α -amino-3-hydroxyl-5-methyl-4-isoxazole-propionate (AMPA) receptor and the *N*-methyl *D*-aspartate (NMDA) receptor, in the postsynaptic membrane. An increased ratio of AMPA receptors to NMDA receptors appears to result in LTP, whereas a decreased ratio results in LTD [26]. Both changes imply alterations in the synthesis of the receptor proteins and in their incorporation into (or removal from) the postsynaptic membrane. In contrast, pre-synaptic LTP and LTD result from increase or decrease, respectively, of release of neurotransmitter from the pre-synaptic terminal. These changes involve alterations in the adenylate cyclase \rightarrow cAMP \rightarrow protein kinase A signal cascade.

Once again, as noted earlier with respect to the intracellular adaptive changes, such alterations of synaptic function are not produced only by chronic drug exposure. They are basic parts of the processes of learning, memory and forgetting (elimination of a memory). An abundance of evidence has shown the involvement of NMDA-receptor-dependent LTP in associative learning, recognition memory and extinction of learned behaviours such as fear and anxiety responses [28–31]. Conversely, transgenic mice deficient in NMDA-receptor-dependent LTD have impaired behavioural flexibility, apparently because of an inability to 'unlearn' previously acquired behaviours that may be in conflict with the learning of a new behaviour [32]. Other parts of the cell signalling mechanisms, including MAPK, ERK and other protein kinases have also been shown to be involved in long-term memory and in related changes in neuronal excitability. Similarly, accumulation of the transcription factor deltaFosB and suppression of *c-fos*, which has been seen after chronic exposure to cocaine or amphetamine, has also been found after exposure to natural reinforcers such as sucrose or sex [33,34].

Again, therefore, it seems self-evident that functions linking one neurone to another, like the functions within single neurones, are mediated by the signalling and response machinery with which neurones are endowed. If a behavioural change, whether drug-related or otherwise, involves synaptic changes between cells, it must obviously involve the machinery with which the cells are equipped. Knowledge of these mechanisms can tell us *how* the change is brought about, but not *why*.

DOPAMINE AND THE 'REWARD SYSTEM'

Not only in the scientific literature, but even in the popular press, it has become the accepted dogma that people take drugs such as nicotine, alcohol, cannabis, heroin, cocaine and amphetamines because all of these potentially addictive substances act on certain cells in the

ventral tegmental area (VTA) of the brainstem, causing them to release increased amounts of dopamine at their axon terminals, resulting in the production of a pleasurable or rewarding state in the user. This 'reward' is presumed to be what motivates the first-time user to repeat the drug-taking experience, and thus to incur the risk of becoming dependent.

All such drugs have indeed been shown to act on various parts of these dopamine-containing cells, causing them to release dopamine from their axonal terminals onto cells in the nucleus accumbens and in the prefrontal cortex that have specific dopamine receptors [27,35,36]. The various drugs do so by different means, but with similar end results [37]. For example, opioid drugs act through opioid receptors on certain interneurons that release the inhibitory transmitter gamma aminobutyric acid (GABA) on to the dopamine-producing cell bodies in the VTA or on their nerve endings in the nucleus accumbens. The opioids inhibit the release of GABA and thus disinhibit the dopamine-releasing cells, so that they release more dopamine. Ethanol may similarly disinhibit the VTA dopamine neurones by removing the inhibitory influence of noradrenaline. In contrast, cocaine and amphetamine act directly on the dopaminergic nerve endings to increase the net release of dopamine in the nucleus accumbens. In all cases, however, the end result is an increase in dopamine activity in the nucleus accumbens and prefrontal cortex.

This 'reward system' was first identified by its responses to natural reinforcers such as food in a hungry animal or water in a thirsty one, or to electrical self-stimulation via electrodes implanted in certain pathways in the brain. Drug reinforcers can give rise to apparent sensitization of the drug effect on the mesolimbic dopaminergic pathways, which is thought to lead to progressively more intense and more persistent drug self-administration. This sensitization has been attributed to synaptic plasticity in the mesolimbic dopaminergic pathways [38,39], or to a qualitative change in the drug effect that is said to give rise to an allostatic rather than a homeostatic response [40]. What might constitute such a qualitative change must be investigated in animals that self-administer the drug, and even in such models there may be confusion with qualitative changes produced by the drug itself when administered by the investigator. For example, in animals that have been made physically dependent on opioids, the action of an opioid on the dopamine neurones in the VTA causes the latter to respond not through the dopaminergic pathway to the nucleus accumbens but through a non-dopaminergic pathway to the pedunculopontine nucleus [41]. In this example the opioids were not self-administered by the animals, so that the change in cell response cannot be part of the process of addiction, although it may help to

explain neuronal responses involved in tolerance and physical dependence.

There is a substantial amount of evidence, moreover, which suggests that the release of dopamine is not a reward mechanism *per se*, but rather a process that arouses and alerts the brain to new or novel stimuli arising from the internal or external environment [42]. These stimuli are not always related to potential rewards. Some motivationally neutral but intense novel stimuli, and in some cases even punishing or aversive stimuli, can be associated with increased dopamine release [43]. Moreover, dopamine neurones in the VTA can emit various types of responses, differing in latency, duration and direction, to different types of stimuli. Schultz [44,45] has amassed a great deal of evidence indicating that there are in fact a number of different kinds of response made by VTA dopamine neurones to different kinds of stimulus, and he suggests that the role of the dopamine neurones in relation to reward is to assess the difference between an anticipated reward and the experienced reward. This assessment would then serve as the basis of experiential learning.

For example, when an animal experiences an unanticipated reward in the presence of previously non-significant stimuli, the reward elicits a large response by the midbrain dopamine neurones; but with repeated pairing of the same cues with the reward, the dopamine release becomes steadily greater in response to the cues that *predict* the reward and steadily less to the reward itself. In addition, reward-predictive cues were found to enhance the strength of excitatory synaptic inputs on the VTA dopamine neurones [46]; this is a specific example of the type of neuroplasticity described above [39]. If the experienced reward matches the prediction in time and intensity, the reward stops eliciting any dopamine increase, and if the reward fails to match the prediction the dopamine output actually decreases [45].

Numerous other neurotransmitters interact with the dopaminergic pathway from the VTA to the nucleus accumbens [37]. In addition to inhibitory projections from noradrenergic and opioidergic nuclei mentioned earlier, there are inhibitory serotonergic fibres from the raphe nuclei to the nucleus accumbens, inhibitory GABA-releasing fibres from the nucleus accumbens back to the VTA, excitatory glutamatergic fibres from the prefrontal cortex and the stria terminalis to the VTA and from the hippocampus to the nucleus accumbens, and excitatory orexinergic fibres from the hypothalamus to the VTA. There are also excitatory CB1 cannabinoid receptors on the VTA neurones themselves, which respond to endocannabinoids produced *in situ* [47] or to exogenous cannabinoids. With such a complex set of interconnections, it is clear that the activity in the nucleus accumbens depends not only on dopamine

release, but on the interplay of all of these neurotransmitters and neuromodulators, as well as others that have not yet been as well characterized.

The cognitive experience of positive reinforcing effects versus punishing aversive effects occurs presumably at some distal site downstream from the alerting effect of dopamine, but there is no persuasive evidence pointing to a single most probable site or mechanism. Modern functional magnetic resonance imaging (fMRI) techniques are being used widely in efforts to identify the probable site, and they have certainly pointed to a number of fore-brain areas that appear to be activated during drug self-administration, but as Vengeliene *et al.* [17] have pointed out, after prolonged alcohol consumption practically all central neurotransmission seems to be affected. Moreover, fMRI may identify which regions or structures are activated during a given behaviour or set of stimuli [48], but in light of the complex neuronal interconnections described above, the occurrence of activity in a given area or pathway does not reveal whether the activity is primary or secondary to activity in some other structure.

A further problem is that equating 'reward' with motivation for drug use, although seemingly a reasonable concept, is almost certainly too simple. It has been known for many years that under certain circumstances experimental animals and humans will press a lever to self-administer an electric shock or other painful stimulus that is ordinarily aversive [49,50]. One may postulate that under conditions of paucity of external stimulation the animal experiences something akin to boredom and that in this state it finds even a painful stimulus somehow rewarding, but that is at best an anthropomorphic conjecture.

Therefore, the whole concept of the dopaminergic mesolimbic and mesocortical pathways as a 'reward system' must be regarded as a convenient label rather than literal fact, and it provides no insight into the reasons why some drug users become addicted while the great majority of users, in whom the drugs also stimulate dopamine release in the nucleus accumbens, never pass from use to compulsive use. A more recent hypothesis is that these drugs also modulate brain stress and antistress mechanisms involving such factors as corticotrophin-releasing factor, orexin, neuropeptide Y, nociceptin and others, and that both positive and negative reinforcement by drug-taking enter into the generation of addiction [51]. This is clearly a more comprehensive approach than focusing exclusively on dopaminergic mechanisms, but the same actions of these drugs can be elicited when they are administered by the experimenter rather than self-administered by the animal.

Recent clinical observations have shown that treatment of Parkinson's disease with drugs that act directly as agonists on dopamine receptors can induce compulsive

behaviours in a small percentage of patients, but in some it takes the form of compulsive eating, in others compulsive sex, and in still others compulsive gambling [52], rather than compulsive self-administration of the drugs. Although opinions differ on whether compulsive eating and compulsive sexual activity should be interpreted as addiction, there is some evidence that they are associated with the same responses in the brain 'reward system' as drug addiction [53–56]. It is therefore necessary to reconsider whether there is anything unique in the addictiveness of drugs as opposed to natural reinforcers.

GENETIC ASPECTS OF ADDICTION

It has been known for centuries that alcoholism runs in families, but it is only since the middle of the 20th century that evidence from twin studies, adoption studies and family pedigrees has demonstrated clearly a genetic component to this familial incidence. Within the past decade or so, comparable evidence has begun to accumulate with respect to addiction to other drugs, including opioids, cocaine, other central stimulants, sedatives, nicotine and cannabis. As there is much more information available for alcohol, however, this discussion will concentrate on alcohol.

Early studies of the genetic mechanisms involved were directed mainly to the enzymes metabolizing alcohol and acetaldehyde, because these enzymes exist in multiple forms which differ greatly in their rates of metabolism of their respective substrates. Special interest attached to the very low-activity form of acetaldehyde dehydrogenase, because individuals homozygous for this form (about 10% of Oriental populations) suffer a severe disulfiram-like reaction on drinking alcohol, characterized by nausea, severe headache and even vascular collapse [57]. This highly aversive reaction appears to protect its bearers against the risk of alcoholism [58]. However, the much more numerous heterozygous individuals have a milder form of this reaction, and social and other pressures can induce them to drink alcohol despite the reaction, even to the point of becoming alcoholic.

Most of the recent studies, both in humans and in laboratory animals, have focused on genes related to individual components of potential vulnerability to become addicted. Starting with standard strains of laboratory rat, several groups have bred lines selectively which differ strikingly in voluntary consumption of alcohol, such as the UchA (low drinker) and UchB (high drinker) lines [59] and the Alko drinker (AA) and non-drinker (ANA) lines [60]. Perhaps the most thoroughly explored such lines are the P (alcohol-preferring) and NP (non-preferring) lines, which have been used widely to study genetic influences on alcohol intake and effects [61]. It

was found later that the P rats also self-administer nicotine much more than do the NP rats, that they lose the nicotine-seeking behaviour less readily than the NP and that when given a small dose of nicotine they relapse into nicotine self-administration much more readily [62]. On the other hand, the P and NP do not differ with respect to cocaine self-administration, but do differ with respect to self-administration of sweet sugar solutions, which have no known drug actions.

Literally hundreds of genes have been identified that may contribute individually to increased vulnerability to drug use and drug addiction, some more than others. Some of these genes appear to be associated statistically with behavioural or personality traits that are associated with increased risk of addiction to various drugs. For example, many (but not all) studies have found that impulsivity (defined as decreased ability to inhibit behavioural responses voluntarily when it would be advantageous to do so) predicts increased consumption of alcohol, both in humans and in mice and other experimental animals, and also predicts greater risk of relapse in those who have undergone extinction of dependent drinking [63]. In recent studies impulsivity was found to be correlated with reduced numbers of dopamine D2/3 receptors in the nucleus accumbens, more rapid acquisition of cocaine self-administration [64] and greater risk of continuing to self-administer cocaine even when this behaviour was punished by electric shock [65]. However, impulsivity has also been found to be influenced strongly by serotonin, and other neurotransmitters and modulators probably also affect it [63]. Impulsivity is also manifested in a variety of other behaviours that are not related specifically to addiction. The nature of the connection between impulsivity and addiction therefore is still unclear.

It must be remembered that a gene does not encode a trait; it encodes RNA for synthesis of a specific protein, either the dominant form of that protein or a structural variant of it. For many of the genes that have been correlated with a behavioural trait the protein product has not yet been identified, and for most of those gene products that have been identified, the mechanistic relation to the trait is not known. It is also highly probable that for most behavioural traits several different gene products play a role in the generation of a single trait. In addition, genes are not necessarily continuously active, i.e. they may be switched on ('expressed') or off under different circumstances. The pattern of protein expression in the nucleus accumbens of alcohol-preferring P rats, for example, is quite different when they self-administer alcohol on their own schedule during continuous access than when they consume the same total amount but during limited-duration drinking periods scheduled by the investigators [66].

There are now numerous examples of environmental factors controlling the expression of genes, so that an individual with a given genetic make-up may be vulnerable to induction of addiction or relapse under some circumstances and not under others. For example, both clinical observations and experimental models have demonstrated that addicted individuals, after undergoing successful extinction of heavy drinking behaviour, experience a greater risk of relapse when exposed to stress [67]. They presumably have the same genetic make-up at all times, but various genes related to vulnerability appear to be switched on when they are under stress and not in its absence.

WHAT CAN ALL THIS TELL US ABOUT ADDICTION?

It is self-evident that a drug alone does not cause addiction because the great majority of those who experience its effects do not become addicted, even if the drug is one that is regarded as 'highly addictive', such as heroin or cocaine. Only some users become addicted, and much research is directed towards learning what factors determine greater or lesser vulnerability of different individuals or populations.

Neurobiological studies have identified a very large number of cellular and synaptic changes that occur in relation to the acute and chronic administration of potentially addicting drugs. As noted above, the changes that have been studied involve the basic machinery of neurones, including practically every neurotransmitter, many cell membrane receptors, enzymes, ion channels, intracellular signalling systems, immediate early genes, gene expression, protein synthesis and so on. The neurobiological changes are consistent with Mark Keller's famous dictum that in alcoholism everything that one measures is either increased or decreased [68]. All one can conclude is that the occurrence of so many changes is indicative of the very widespread involvement of many different nuclei and pathways in the actions of drugs. Many of the changes are probably secondary to the drug actions, or may be part of the adaptive responses underlying tolerance and physical dependence; but unless they are specifically linked to self-administration, they may not tell us much about the generation and expression of addiction.

This is still useful information, however, and one cannot agree so readily with Keller's later extension of his original 'Law', that 'Alcoholics are different in so many ways that it makes no difference'. Elucidation of the mechanisms involved in neuronal adaptations to drugs has yielded valuable knowledge about the workings of the brain. It may also suggest pharmacological interventions to prevent the production or function of some of the

gene products that contribute to vulnerability to addiction or relapse, and thus help to maintain treatment-induced abstinence [69]. A useful analogy has been drawn with the workings of a motor vehicle: it takes many hundreds of parts, working as a well-integrated system, to make a car run properly, but knocking out only one essential part can prevent it from running (Y. Israel, personal communication). Naltrexone, acamprosate and buprenorphine are examples that come to mind of agents that block one important part of the integrated system that gives rise to addiction. The problem is that the parts that they block individually are important but not uniquely so, so that none of these agents is certain to halt the dependence completely or permanently [70,71]. Therefore the development of new agents of this type may continue to be a helpful but limited approach to the treatment of addiction. Hope for more effective methods of treatment, and especially of prevention, probably rests on discovering primary causes of addictive behaviour rather than mechanisms by which it is expressed. Causes, in this context, means the factors that set the machinery in motion and, as pointed out earlier, the drug itself is clearly not a sufficient cause.

Exploration of genetic factors will probably also not provide such knowledge, for reasons discussed above. Genes generate the proteins that constitute the building blocks of the cellular mechanisms discussed earlier. Therefore identification of genes linked to addiction carries the analysis of these mechanisms one step deeper, but is still not likely to explain causation. Every behaviour that may contribute to the production of addiction will have a cellular mechanism involving many different genes, and the more that are found the less clear will be the specific role of any single one in the generation and maintenance of addiction. A recent study of the literature encountered 1500 genes linked in some way to addiction; 396 of these were used to construct a map of genes and gene products constituting five major molecular pathways that appear to be common to addiction to various drug classes [72]. The resulting map bears a striking resemblance to the known pathways of cell response to a wide variety of stimuli. Moreover, the fact that gene expression is affected by environmental and contextual factors, as well as by the drugs that are self-administered, means that addiction cannot even be conceptualized exclusively in terms of the interaction between the drugs and the genetic constitution of an individual vulnerable user. A variety of elements of the environmental context must also be taken into account.

For example, sensitization of locomotor activity by cocaine, amphetamine, morphine or low doses of ethanol in rodents is thought to be one manifestation of the postulated 'rewarding' motivational effects of these drugs. However, this sensitization occurs more readily when the

drug is given in a novel environment rather than in the animal's home cage, and the enhancing effect of environmental novelty is most evident when relatively low doses of the drugs are used [73]. A different type of example is provided by Robins *et al.*'s studies of American veterans of the Vietnam War who had returned to the United States as heroin addicts [74]. A surprisingly high proportion of those who became abstinent during treatment have remained abstinent since returning to their normal home environments. This is in striking contrast with Wikler's [75] observations of addicts who had long been free of withdrawal symptoms and drug craving during their confinement in US Public Health Service hospitals, but relapsed abruptly on their return to the environments associated with their previous drug use.

One concludes inevitably that addiction is a behavioural disorder generated within an extremely complex interactive system of drug, individual user, environment and changing circumstances [76]. This is no longer the terrain of pharmacology or neurobiology or psychology or sociology, but an amalgam of all of them. The challenge for research is to find a conceptual framework that can generate the appropriate methods for investigating such an immensely complex system. Science includes two opposite processes, the reductive or analytical process [77] and the integrative or synthetic process. The analytical approach is much the more widely practised, and has unquestionably yielded enormous gains in our understanding of basic mechanisms. In the present context, it has explored the molecular elements that constitute the machinery of living cells and helped to explain how they work. However, to understand how living organisms acquire and perform highly complex behaviours such as drug addiction, under all the various environments and circumstances to which they are exposed, it is necessary to understand how the subcellular, cellular, organ system and whole organism components interact with the external environmental influences. The early hope and promise of neurobiology was that it would do exactly that, and thus explain animal behaviour in its entirety, at all levels of organization. In the case of drug addiction it has not yet done so, and as long as the emphasis remains chiefly on the reductive analytical approach, it cannot do so.

The type of process that is required to explain addiction can perhaps be suggested by an analogy with aeronautical engineering. In order to build an aircraft that will fly successfully, efficiently, rapidly, safely and economically, it is not sufficient to put together a fuselage, wings and a jet motor. It is necessary to take into account the aerodynamics of wing shape, the tensile strength and brittleness of a wide variety of metals and alloys of different densities, the energy generated by combustion of different fuels relative to their weight, the interaction of the

proposed design with atmospheric resistance and turbulence at different altitudes, the ability of humans to monitor and operate all the controls accurately and safely, the ability of the operators to assess the potential market and carry enough passengers at reasonable prices to cover the costs of operation and generate a profit, and so on, with hundreds or thousands of separate contributory types and pieces of information. These must all be studied analytically, but then they must all be integrated into model interactive systems that allow the researchers to predict and explain all aspects of the aircraft's behaviour and responses under all imaginable conditions. This process has been facilitated enormously by the development of highly sophisticated and powerful computer theory and instrumentation.

Similarly, it is inherently impossible to explain addiction by pursuing only the analytical study of drug interactions with the nervous system at ever-finer levels of molecular structure and function. It is also necessary to integrate that knowledge into more and more complex models that include interactions at all levels, from the submolecular to the environmental and social, so that one can test predictions of how the complex system will behave under all the possible influences which are known to modify risk of addiction and of relapse, both in individual cases and in society as a whole. That is a very tall order, but it is not inherently impossible for neurobiologists, sociologists, psychiatrists, pharmacologists, economists and relevant others to tackle the problems of addiction in a manner analogous to the engineers' approach. In the long term, it is likely to be more fruitful than concentrating on a search for medications by studying receptor subtypes or gene variants.

Declaration of interest

None.

Acknowledgement

I am greatly indebted to the following colleagues for their thorough critical reading of the manuscript and their valuable suggestions for improving it: W.A. Corrigan, Y. Israel, A.D. Lê, T.-K. Li, R.F. Mucha and D. Van der Kooy.

References

1. World Health Organization (WHO). *13th Report of the World Health Organization Expert Committee on Drug Dependence. WHO Technical Report Series No. 273*. Geneva: WHO; 1964.
2. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, 4th edn, text revision (DSM-IV-TR). Washington, DC: American Psychiatric Association Publishers; 2000.
3. Clarke P. B. S., Corrigan W. A., Ferrence R. G., Friedland M. L., Kalant H., Kozlowski L. T. *Tobacco, Nicotine, and Addiction*. Report prepared for the Royal Society of Canada. Ottawa: Royal Society of Canada; 1989.
4. Musto D. F. *The American Disease: Origins of Narcotic Control*, 3rd edn. New York: Oxford University Press; 1999.
5. O'Brien C. P., Volkow N., Li T.-K. What's in a word? Addiction versus dependence in DSM-V. *Am J Psychiatry* 2006; **163**: 764–5.
6. Kalant H. Addiction: concepts and definitions. In: Korsmeyer P., Kranzler H. R., editors. *Encyclopedia of Drugs, Alcohol, and Addictive Behaviors*, 3rd edn. Farmington Hills, MI: Macmillan Reference; 2008, p. 19–28.
7. Adrian E. D., Zotterman Y. Impulses produced by sensory nerve-endings: response of a single end-organ. *J Physiol* 1926; **61**: 151–71.
8. LeBlanc E. A., Kalant H., Gibbins R. J. Acute tolerance to ethanol in the rat. *Psychopharmacologia (Berl)* 1975; **41**: 43–6.
9. Radlow R. A. Quantitative theory of acute tolerance to alcohol. *Psychopharmacology* 1994; **114**: 1–8.
10. McQuarrie D. G., Fingl E. Effects of single doses and chronic administration of ethanol on experimental seizures in mice. *J Pharmacol Exp Ther* 1958; **124**: 264–71.
11. Mintzer M. Z., Griffiths R. R. Flumazenil-precipitated withdrawal in healthy volunteers following repeated diazepam exposure. *Psychopharmacology* 2005; **178**: 259–67.
12. Lofwall M. R., Walsh S. L., Bigelow G. E., Strain E. C. Modest opioid withdrawal suppression efficacy of oral tramadol in humans. *Psychopharmacology* 2007; **194**: 381–93.
13. Williams J. T., Christie M. J., Manzoni O. Cellular and synaptic adaptations mediating opioid dependence. *Physiol Rev* 2001; **81**: 299–343.
14. Christie M. J. Cellular neuroadaptations to chronic opioids: tolerance, withdrawal and addiction. *Br J Pharmacol* 2008; **154**: 384–96.
15. Tang L., Shukla P. K., Wang Z. J. Disruption of acute opioid dependence by antisense oligodeoxynucleotides targeting neurogranin. *Brain Res* 2007; **1143**: 78–82.
16. Harris R. A., Trudell J. R., Mihic S. J. Ethanol's molecular targets. *Sci Signal* 2008; **1**: re7.
17. Vengeliene V., Bilbao A., Molander A., Spanagel R. Neuropharmacology of alcohol addiction. *Br J Pharmacol* 2008; **154**: 299–315.
18. Yang X., Wand G. Ethanol uses cAMP-independent signal transduction mechanisms to activate proenkephalin promoter activity in rat C6 glioma cells. *Alcohol Clin Exp Res* 2000; **24**: 952–7.
19. Yuan C., O'Connell R. J., Wilson A., Pietrzykowski A. Z., Treistman S. N. Acute alcohol tolerance is intrinsic to the BKCa protein, but is modulated by the lipid environment. *J Biol Chem* 2008; **283**: 5090–8.
20. Pandey S. C. Neuronal signaling systems and ethanol dependence. *Mol Neurobiol* 1998; **17**: 1–15.
21. Xu M. C-Fos is an intracellular regulator of cocaine-induced long-term changes. *Ann NY Acad Sci* 2008; **1139**: 1–9.
22. Lehner C., Taracha E., Skorzevska A., Turzynska D., Sobolewska A., Maciejak P. *et al.* Expression of c-Fos and CRF in the brains of rats differing in the strength of a fear response. *Behav Brain Res* 2008; **188**: 154–67.
23. Goeldner C., Reiss D., Wichmann J., Meziane H., Kieffer B. L., Ouagazzal A.-M. Nociceptin receptor impairs recognition memory via interaction with NMDA receptor-dependent mitogen-activated protein kinase/extracellular signal-regulated kinase signaling in the hippocampus. *J Neurosci* 2008; **28**: 2190–8.

24. Cohen-Matsliah S. I., Brosh I., Rosenblum K., Barkai E. A novel role for extracellular signal-regulated kinase in maintaining long-term memory-relevant excitability changes. *J Neurosci* 2007; **27**: 12584–9.
25. Shaul Y. D., Seger R. The MEK/ERK cascade: from signaling specificity to diverse functions. *Biochim Biophys Acta* 2007; **1773**: 1213–26.
26. Fischer A., Radulovic M., Schrick C., Sananbenesi F., Godovac-Zimmermann J., Radulovic J. Hippocampal MEK/ERK signaling mediates extinction of contextual freezing behavior. *Neurobiol Learn Mem* 2007; **87**: 149–58.
27. Kauer J. A., Malenka R. C. Synaptic plasticity and addiction. *Nat Rev Neurosci* 2007; **8**: 844–58.
28. Mokin M., Zheng Z., Keifer J. Conversion of silent synapses into the active pool by selective GluR1-3 and GluR4 AMPAR trafficking during *in vitro* classical conditioning. *J Neurophysiol* 2007; **98**: 1278–86.
29. Sotres-Bayon F., Bush D. E. A., LeDoux J. E. Acquisition of fear extinction requires activation of NR2B-containing NMDA receptors in the lateral amygdala. *Neuropsychopharmacology* 2007; **32**: 1929–40.
30. Kopp C., Longordo F., Luthi A. Experience-dependent changes in NMDA receptor composition at mature central synapses. *Neuropharmacology* 2007; **53**: 1–9.
31. Lapointe N. P., Ung R. V., Guertin P. A. Plasticity in sublesionally located neurons following spinal cord injury. *J Neurophysiol* 2007; **98**: 2497–500.
32. Nicholls R. E., Alarcon J. M., Malleret G., Carroll R. C., Grody M., Vronskaya S. *et al.* Transgenic mice lacking NMDAR-dependent LTD exhibit deficits in behavioral flexibility. *Neuron* 2008; **58**: 104–17.
33. Renthal W., Carle T. L., Maze I., Covington H. E. III, Truong H. T., Alibhai I. *et al.* DeltaFosB mediates epigenetic desensitization of the *c-fos* gene after chronic amphetamine exposure. *J Neurosci* 2008; **28**: 7344–9.
34. Wallace D. L., Vialou V., Rios L., Carle-Florence T. L., Chakravarty S., Kumar A. *et al.* The influence of DeltaFosB in the nucleus accumbens on natural reward-related behavior. *J Neurosci* 2008; **28**: 10272–7.
35. Di Chiara G., Imperato A. Drugs abused by humans preferentially increase synaptic dopamine concentrations in the mesolimbic system of freely moving rats. *Proc Natl Acad Sci USA* 1980; **85**: 5274–8.
36. Koob G. F. Drugs of abuse: anatomy, pharmacology and function of reward pathways. *Trends Pharmacol Sci* 1992; **13**: 177–84.
37. Feltenstein M. W., See R. E. The neurocircuitry of addiction: an overview. *Br J Pharmacol* 2008; **154**: 261–74.
38. Brebner K., Wong T. P., Liu L., Liu Y., Campsall P., Gray S. *et al.* Nucleus accumbens long-term depression and the expression of behavioral sensitization. *Science* 2005; **310**: 1340–3.
39. Thomas M. J., Kalivas P. W., Shaham Y. Neuroplasticity in the mesolimbic dopamine system and cocaine addiction. *Br J Pharmacol* 2008; **154**: 327–42.
40. Koob G. F. Alcoholism: allostasis and beyond. *Alcohol Clin Exp Res* 2003; **27**: 232–43.
41. Laviolette S. R., Van der Kooy D. GABA receptors signal bidirectional reward transmission from the ventral tegmental area to the tegmental pedunculo-pontine nucleus as a function of opiate state. *Eur J Neurosci* 2004; **20**: 2179–87.
42. Robinson T. E., Berridge K. C. The neural basis of drug craving: an incentive-sensitization theory of addiction. *Brain Res Rev* 1993; **18**: 247–91.
43. Mirenowicz J., Schultz W. Preferential activation of mid-brain dopamine neurons by appetitive rather than aversive stimuli. *Nature* 1996; **379**: 449–51.
44. Schultz W. Multiple dopamine functions at different time courses. *Annu Rev Neurosci* 2007; **30**: 259–88.
45. Schultz W. Behavioral dopamine signals. *Trends Neurosci* 2007; **30**: 203–10.
46. Stuber G. D., Klanker M., de Ridder B., Bowers M. S., Joosten R. N., Feenstra M. G. *et al.* Reward-predictive cues enhance excitatory synaptic strength onto midbrain dopamine neurons. *Science* 2008; **321**: 1690–2.
47. Solinas M., Goldberg S. R., Piomelli D. The endocannabinoid system in brain reward processes. *Br J Pharmacol* 2008; **154**: 369–83.
48. Logothetis N. K. What we can do and what we cannot do with fMRI. *Nature* 2008; **453**: 869–78.
49. Speakman R. D., Kelleher R. T. Behavioral effects of self-administered cocaine: responding maintained alternately by cocaine and electric shock in squirrel monkeys. *J Pharmacol Exp Ther* 1979; **210**: 206–14.
50. Belvedere E., Pasewark R. A. Conformity and modeling in an aversive task. *J Clin Psychol* 1976; **32**: 265–7.
51. Koob G. F. A role for brain stress systems in addiction. *Neuron* 2008; **59**: 11–34.
52. Dodd M. L., Klos K. J., Bower J. H., Geda Y. E., Josephs K. A., Ahlskog J. E. Pathological gambling caused by drugs used to treat Parkinson disease. *Arch Neurol* 2005; **62**: 1–5.
53. Corwin R. L., Grigson P. S. Symposium overview—food addiction: fact or fiction? *J Nutr* 2009; **139**: 617–19.
54. Rogers P. J., Smit H. J. Food craving and food 'addiction': a critical review of the evidence from a biopsychosocial perspective. *Pharmacol Biochem Behav* 2000; **66**: 3–14.
55. Blum K., Braverman E. R., Holder J. M., Lubar J. F., Monastero V. J., Miller D. *et al.* Reward deficiency syndrome: a biogenetic model for the diagnosis and treatment of impulsive, addictive, and compulsive behaviors. *J Psychoact Drugs* 2000; **32**(Suppl i–iv): 1–112.
56. Keane H. Disorders of desire: addiction and problems of intimacy. *J Med Hum* 2004; **25**: 189–204.
57. Li T.-K., Bosron W. F. Genetic variability of enzymes of alcohol metabolism in human beings. *Ann Emerg Med* 1986; **15**: 997–1004.
58. Li T.-K. Pharmacogenetics of responses to alcohol and genes that influence alcohol drinking. *J Stud Alcohol* 2000; **61**: 5–12.
59. Mardones J., Segovia-Riquelme N. Thirty-two years of selection of rats by ethanol preference: UChA and UChB strains. *Neurobehav Toxicol Teratol* 1983; **5**: 171–8.
60. Eriksson K. Genetic selection for voluntary alcohol consumption in albino rats. *Science* 1968; **161**: 739–41.
61. Li T.-K., Lumeng L., Doolittle D. P. Selective breeding for alcohol preference and related responses. *Behav Genet* 1993; **23**: 163–70.
62. Lê A. D., Li Z., Funk D., Shram M., Li T.-K., Shaham Y. Increased vulnerability to nicotine self-administration and relapse in alcohol-naïve offspring of rats selectively bred for high alcohol intake. *J Neurosci* 2006; **26**: 1872–9.
63. Poulos C. X., Parker J. L., Lê A. D. Dexfenfluramine and 8-OH-DPAT modulate impulsivity in a delay-of-reward paradigm: implications for a correspondence with alcohol consumption. *Behav Pharmacol* 1996; **7**: 395–9.
64. Dalley J. W., Fryer T. D., Brichard L., Robinson E. S. J., Theobald D. E. H., Lääne K. *et al.* Nucleus accumbens D2/3

- receptors predict trait impulsivity and cocaine reinforcement. *Science* 2007; **315**: 1267–70.
65. Belin D., Mar A. C., Dalley J. W., Robbins T. W., Everitt B. J. High impulsivity predicts the switch to compulsive cocaine-taking. *Science* 2008; **320**: 1352–5.
 66. Bell R. L., Kimpel M. W., Rodd Z. A., Strother W. N., Bai F., Peper C. L. *et al.* Protein expression changes in the nucleus accumbens and amygdala of inbred alcohol-preferring rats given either continuous or scheduled access to ethanol. *Alcohol* 2006; **40**: 3–17.
 67. Breese G. R., Chu K., Dayas C. V., Funk D., Knapp D. J., Koob D. F. *et al.* Stress enhancement of craving during sobriety: a risk for relapse. *Alcohol Clin Exp Res* 2005; **29**: 185–95.
 68. Keller M. The oddities of alcoholics. *Q J Stud Alcohol* 1972; **33**: 1147–8.
 69. Wallner M., Olsen R. W. Physiology and pharmacology of alcohol: the imidazobenzodiazepine alcohol antagonist site on subtypes of GABA receptors as an opportunity for drug development? *Br J Pharmacol* 2008; **154**: 288–98.
 70. Mason B. J. Acamprosate and naltrexone treatment for alcohol dependence. *Eur Neuropsychopharmacol* 2003; **13**: 469–75.
 71. Anton R., O'Malley S., Ciraulo D. A., Cisler R. A., Couper D., Donovan D. M. *et al.* Combined pharmacotherapies and behavioral interventions for alcohol dependence. The COMBINE study: a randomized clinical trial. *JAMA* 2006; **295**: 2003–17.
 72. Li C.-Y., Mao X., Wei L. Genes and (common) pathways underlying addiction. *PLoS Comput Biol* 2008; **4**: e2.
 73. Badiana A., Robinson T. E. Drug-induced neurobehavioral plasticity: the role of environmental context. *Behav Pharmacol* 2004; **15**: 327–39.
 74. Robins L. N., Helzer J. E., Davis D. H. Narcotic use in Southeast Asia and afterward: an interview study of 898 Vietnam returnees. *Arch Gen Psychiatry* 1975; **32**: 955–61.
 75. Wikler A. Narcotics. In: Braceland F. J., editor. *The Effect of Pharmacologic Agents on the Nervous System*. Baltimore, MD: Williams & Wilkins; 1959, p. 334–55.
 76. Edwards G. Addiction, reductionism and Aaron's rod. *Addiction* 1994; **89**: 9–12.
 77. Stanford University. Reductionism in biology. *Stanford Encyclopedia of Philosophy*. Available at: <http://plato.stanford.edu/archives/spr2009/entries/reduction-biology/> (accessed 30 April 2009).