OPINION

Differentiating the rapid actions of cocaine

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Abstract | The subjective effects of intravenous cocaine are felt almost immediately, and this immediacy plays an important part in the drug's rewarding impact. The primary rewarding effect of cocaine involves blockade of dopamine reuptake; however, the onset of this action is too late to account for the drug's initial effects. Recent studies suggest that cocaine-predictive cues — including peripheral interoceptive cues generated by cocaine itself — come to cause more direct and earlier reward signalling by activating excitatory inputs to the dopamine system. The conditioned activation of the dopamine system by cocaine-predictive cues offers a new target for potential addiction therapies.

The speed with which cocaine activates the reward circuitry of the brain is thought to be an important determinant of the drug's addictive potency (BOX 1). Speed of delivery is important for all rewards[1]; the effectiveness of a reward can be decreased by half or more if it is delayed by a mere second or two[2,3]. It is widely assumed from the short latency of subjective and behavioural responses to intravenous cocaine injections, that the drug almost instantly activates the reward system in the brain. However, experienced users report cocaine-like subjective effects within seconds, before the drug has time to reach the brain, cross the blood–brain barrier and interact with its central pharmacological targets[4].

The primary rewarding effects of cocaine result from its ability to augment the actions of dopamine by inhibiting its reuptake by the dopamine transporter[5–7], and thus prolonging its effects in regions to which the dopamine system projects[8–10]. However, blockade of the dopamine transporter by intravenous cocaine has a latency of several seconds in the rat, and longer in humans; it takes cocaine about 15 seconds to reach the brain from intravenous injection in the arm. Thus, the acute central actions of cocaine cannot explain the drug's immediate effects after intravenous injection.

Recent findings indicate that some peripheral action of cocaine — such as the blockade of potassium channels in the sensory nerves of the cardiovascular system[11–13] — is sensed and relayed trans-synaptically to the brain, where, in parallel with external reward-predictive cues, it comes to briefly activate the reward system of cocaine-experienced rats through Pavlovian conditioning[14,15,16].

Here, we describe and contrast two rewarding effects of cocaine in the dopamine system: the well-known, unconditioned rewarding effect resulting from the blockade of the dopamine reuptake mechanism in the CNS and the more immediate (though weaker), conditioned dopamine-activating effect resulting from cocaine's ability to trigger conditioned excitatory input to the brain from the periphery. Although attempts to develop pharmacotherapies for cocaine addiction have mainly focused on the effect of the drug within the reward circuitry of the brain[17], the fact that reward-predicting stimuli have more immediate effects and can activate the reward system even in the absence of the reward itself[14] suggests that peripheral sites of cocaine act as potential targets for addiction medication.

Cocaine's fast rewarding action

The primary rewarding effects of cocaine and related drugs are unconditioned and can thus be seen in animals that have no prior experience with the drug[8,9,18]. In cocaine-naive animals, the rewarding effect of cocaine results from the drug's ability to elevate extracellular levels of the neurotransmitter dopamine; dopamine levels are elevated several-fold during periods when rats[19] or monkeys[20] are allowed to lever-press for intravenous cocaine (cocaine 'self-administration'). The timing of successive lever-presses in a session can be predicted from the rise and fall of extracellular dopamine in the forebrain; the next response occurs when the elevated dopamine level from the previous injection falls back to a characteristic 'trigger-point'[21]. If the postsynaptic signalling effects of extracellular dopamine are blocked[22–24] or if the mesocorticolimbic dopamine system is lesioned[25–27], cocaine loses its ability to maintain the self-administration habit.

Three brain targets for the rewarding actions of cocaine have been identified. Cocaine is rewarding when microinjected directly into the medial prefrontal cortex[8], the ventromedial shell of nucleus accumbens[9] or the adjacent medial portion of the olfactory tubercle[10]. Perhaps because it has been suggested to provide an interface between the mechanisms of motivation and motor function[28], the nucleus accumbens has received the most extensive study. Although cocaine elevates dopamine levels in both the core and the shell of nucleus accumbens, the elevation is stronger and more immediate in the shell[29,30], where rewarding effects of the drug have been shown[9,10].

Extracellular dopamine levels can be elevated either by an increase in dopamine release or by a decrease in dopamine reuptake. Amphetamine has both effects: it causes dopamine release and it blocks dopamine reuptake[31]. Cocaine also blocks dopamine uptake but does not cause dopamine release, at least *in vitro*[5]. Thus, until recently[30,32,33], cocaine has been known as a dopamine reuptake inhibitor and not a dopamine releaser[5,34]. Consistent with this view, cocaine does not cause the increase in metabolite levels that would be caused by increased dopamine release[34]. Although an early report suggested that knockout mice lacking the dopamine transporter could still learn to self-administer cocaine[35], this finding has not been replicated[7]. The emerging consensus is that any minimal signs of cocaine self-administration in such mice reflect the ability of cocaine to block dopamine uptake by other monoamine transporters[7,36] that take over the task of dopamine clearance when the dopamine transporter is deleted. Similar mechanisms probably take place in brain regions where the dopamine transporter is sparse[37–39]. Thus, the blockade of dopamine uptake remains the widely accepted mechanism for cocaine's unconditioned rewarding action.

> “the fast pharmacological action of cocaine in the central nervous system — the blockade of dopamine reuptake — becomes important after tens of seconds and does not seem to explain the ultra-fast subjective and behavioural effects of the drug”

Fast-scan cyclic voltammetry (BOX 2) can reveal the dopamine concentration in the brain and has the temporal resolution needed to determine the onset of the central effects of intravenous cocaine. It has been used in two ways, each of which has suggested that cocaine has very rapid effects. In the first approach, spontaneous fluctuations in dopamine level are monitored before and after intravenous cocaine or saline injections in freely moving rats[30,40,41]. This approach shows that intravenous cocaine can cause significant increases in dopamine signalling in the shell of nucleus accumbens in as little as 8 seconds after the onset of the injection[30]. However, similar early increases are not seen in the core of nucleus accumbens[30], where blockade of dopamine reuptake by cocaine should be more evident because the density of dopamine transporters is greater[42]. Clear evidence of cocaine-induced changes in dopamine levels in the core of cocaine-naive rats are seen only 30–40 seconds after intravenous injection[30,40], and the dopamine elevations seen in the first 10 seconds or so in the shell seem to reflect cocaine's effects on dopaminergic neuronal firing[33] rather than on dopamine reuptake[30].

In the second approach, dopamine release in the core of nucleus accumbens was triggered by electrical stimulation of the cell bodies in the ventral tegmental area, and the clearance of the stimulated release was estimated from the rate of decay of the voltammetric peak that reflects the dopamine concentration. From this approach it was suggested that intravenous cocaine starts to block dopamine uptake in as little as 4 seconds after the onset of the intravenous injection[43]. However, this estimate of ultra-fast uptake inhibition is based on a model that assumes the only source of dopamine release to be the stimulation applied by the experimenter[44]; this assumption is now open to question[16,30,33]. In any case, accumulation of a physiologically significant amount of dopamine, through this or any other mechanism, seems to take at least 8 and up to perhaps 40 seconds in animals having no prior experience with cocaine[30,40]. Thus, the fast pharmacological action of cocaine in the central nervous system — the blockade of dopamine reuptake — becomes important after tens of seconds and does not seem to explain the ultra-fast subjective and behavioural effects of the drug, effects that are seen in the initial seconds after onset of an intravenous cocaine injection and unquestionably before the drug reaches the brain in the case of human subjects.

Box 1 | **The importance of speed**

The speed with which rewards are delivered contributes importantly to their effectiveness. Thus, rats learn first and run fastest in the portions of a maze that are closest to the reward[63]. More direct evidence comes from studies in which the subject is given the choice between an immediate and a delayed reward; the immediate reward is preferred to the delayed reward even when the delayed reward is somewhat larger[64]. Economic theory proposed that the effect of delay was exponential[65], but experimental evidence suggests a hyperbolic decay function[3,66].

Differing delays in reward are thought to explain why some drugs and routes of drug administration are more addictive than others. For example, heroin — which is highly addictive — enters the brain more rapidly but activates the same receptor as the less addictive methadone that is used in treatment[67]. Similarly, nicotine is more addictive and reaches the brain faster when tobacco is smoked than when the leaf is chewed or when nicotine itself is given by the transdermal nicotine patch[68]. Likewise, the speed with which smoked or intravenous cocaine reaches the brain is thought to contribute importantly to the greater addictive potency of these routes of administration over intranasal or oral routes[69].

Cocaine's ultra-fast rewarding action

More immediate activation of the dopamine system occurs when the reward is reliably predicted by environmental stimuli. Electrophysiological studies of food reward in monkeys have revealed that reward predictors can activate the dopamine system before the receipt of the reward itself[45]. Early in training, the taste of juice or a piece of apple activates the dopamine system of a hungry monkey; however, after sufficient training the dopamine system comes to be activated when the monkey hears a predictor, such as the click associated with the unlatching of the door between the monkey and the piece of apple[45]. Once its reward-predictive meaning is learned, the click activates the dopamine system and the rewarding food itself fails to do so. This reward-predictive dopamine release occurs a second or two earlier than the actual presentation of the food reward[45]. Reliable reward-predictors cause an ultra-fast accumulation (1–3 seconds) of extracellular dopamine; this is a conditioned response to what was an initially ineffective stimulus, a stimulus that has gained importance by its Pavlovian association with the reward it predicts[40,46].

Similarly, activation of the dopamine system is seen before each earned cocaine injection in rats that have learned to self-administer cocaine by lever-pressing[47,48]. Here, the initial dopamine elevation is seen as a brief peak, 1 or 2 seconds before the lever-press, as the rat starts to move towards the lever (FIG. 1). This initial peak is not in response to any external stimulus change; however, the peak and the movement are both cocaine predictors in their own right.

Further dopamine release associated with reward-predictive events is triggered by the consequences of the lever-press[47,48]. The lever-press typically results in several reward-predictive cues: the click of the lever, often a 'cue' light or an auditory signal, or both, and then the temperature and pressure of the injection (the injection is usually at room — not body — temperature), and other peripheral cues of the drug itself. These events cause dopamine elevations that start in the first second after the lever-press; the early post-response surge, often with one or two clear peaks, returns to baseline in approximately 5 seconds[40,47]. This ultra-fast surge in dopamine concentration is confirmed as a conditioned response (or a composite of several conditioned responses) to cocaine-predictive stimuli in several ways. First, and most importantly, it is not seen in cocaine-naive animals; it is not simply an unconditioned response to the various sensory events[46,47]. Second, it develops progressively with repeated pairings of the stimuli with the cocaine injections[46]. Finally, it is progressively lost under extinction conditions, during which the animal learns that the stimuli that were once predictive of rewarding cocaine are now predictive of non-rewarding saline[48].

Thus, reward-predictive conditioned stimuli begin to elevate extracellular dopamine levels; they do so by activating dopaminergic neurons[14] and they do so before the time that the initial pharmacological action of cocaine affects the reward system in cocaine-naive animals[40]. This is most clearly shown using food reward and extracellular electrophysiological recordings taken from dopaminergic neurons in behaving animals to differentiate the receipt of reward predictors from receipt of the reward itself[14]. In the case of intravenous cocaine reward, the reward itself is not seen or smelt or tasted, and thus its precise onset is more difficult to identify; indeed, it is only reward predictors that reach the primary senses in the case of intravenous drug reward[49]. Nonetheless, it is clear from voltammetry data that an ultra-fast response to cocaine-predictive cues reaches the reward system in the first 5 seconds after cocaine injections in cocaine-trained animals, whereas the fast, unconditioned dopamine elevations caused by the central actions of cocaine in cocaine-naive (untrained) animals only become evident some seconds later[30,40,41].

Box 2 | Measuring and accounting for the latency of central drug effects

Various methods exist to detect the effects of cocaine on dopamine levels in behaving animals; however, *in vivo* voltammetry[70] has the best temporal resolution of these approaches. This method involves electrochemical detection of dopamine from its oxidation and reduction currents, and offers sub-second resolution of dopamine fluctuations[71]. However, several factors other than the speed of detection are involved in estimating the time between the onset of an intravenous injection and the onset of the central pharmacological effects of the injected drug. The speed of injection is an obvious factor in how quickly the drug reaches the brain in pharmacological concentration; injection times in intravenous drug self-administration studies range from as little as 1 or 2 seconds[72] to as much as 1 or 2 minutes[73,74]. Rapid injections are more likely to have non-pharmacological effects related to pressure, osmolarity and temperature change (as a drug is usually injected at room — not body — temperature). The concentration of the drug in the syringe will also affect how quickly pharmacological concentrations are reached in the blood. Once in the blood, the speed with which pharmacological concentrations reach the brain will depend on the distance of the injection site from the brain (in the order of cm in humans and mm in rodents) and the heart rate and blood pressure, which may in turn be a function of the speed of injection. In the case of cocaine, it must still cross the blood–brain barrier and then diffuse and bind to the dopamine transporter before dopamine uptake is blocked. Once the transporter is blocked it will take some time for extracellular dopamine to accumulate to the detection level of the measurement device. Thus, the time between the onset of an intravenous injection and the detection of a central pharmacological effect is not instantaneous, and a confidence interval of 1 or 2 seconds is likely to be appropriate in any given experiment.

Dual rewarding effects of cocaine

In experienced users, the net rewarding effects of cocaine reflect not only the central pharmacological effect of the drug but also a substantial contribution from reward-predictive conditioned stimuli. The reward-predictive inputs from environmental stimuli trans-synaptically activate the reward system[46,50] and thus make an independent set of contributions to reward function in trained animals. They become conditioned reinforcers, stimuli that prolong extinction and that can serve to establish new habits in their own right[51].

Input from cocaine-predictive stimuli reaches the dopamine system partly through excitatory glutamatergic[15] and cholinergic[52] afferents. Glutamate and acetylcholine are released in the ventral tegmental area during periods of cocaine self-administration[15,52], and in each case the initial release is approximately the same whether lever-pressing causes the expected cocaine injection or an unexpected saline injection[15,52]. This indicates that the initial response has more to do with what the animal is expecting than with what the animal actually receives. Glutamate input to the ventral tegmental area activates the dopamine system, causing dendritic dopamine release (an index of dopaminergic impulse flow[53,54]) that is blocked by local infusion of an ionotropic glutamate receptor antagonist[16,55]. Glutamate levels and acetylcholine levels remain higher in animals self-administering cocaine than in animals self-administering saline, and a compensatory increase in cocaine intake is seen when either glutamate[15] or acetylcholine[52] receptors in the ventral tegmental area are blocked, suggesting that ventral tegmental release of glutamate and acetylcholine each contribute to the total rewarding impact of expected and earned cocaine injections[15,52].

Thus, there are two rewarding effects of expected cocaine injections: fast, unconditioned reward (blockade of cocaine reuptake) and ultra-fast, conditioned reward (input-triggered dopamine release). Interestingly, a peripheral stimulus effect of cocaine itself serves as a conditioned stimulus for ventral tegmental glutamate release and dopaminergic activation[16]. In rats trained to self-administer regular cocaine (cocaine hydrochloride, which readily crosses the blood–brain barrier), cocaine methiodide (a cocaine analogue that does not cross the barrier) causes the same glutamate release and dopaminergic activation as in the first minutes of self-administration of regular cocaine. Cocaine methiodide has no such effect in cocaine-naive rats — rats that have not learned to expect the central effects of cocaine immediately following the peripheral effects of the drug[16]. Thus, in cocaine-experienced rats, the peripheral effects of cocaine come to predict the central rewarding effects of cocaine, and — like predictive external cues — cause conditioned dopamine release. Because these conditioned effects have been identified with microdialysis — which has poor temporal resolution — their latency is not precisely known. It is understood, however, that an intravenous injection of cocaine methiodide can affect dopaminergic (and other) neurons in the brain within a few seconds[33,56].

> “Interestingly, a peripheral stimulus effect of cocaine itself serves as a conditioned stimulus for ventral tegmental glutamate release and dopaminergic activation.”

Examination of the decay of the early dopamine peak (first 5 seconds) following the lever-press under extinction conditions suggests that the effect of the conditioned contribution of peripheral cocaine cues may itself be an ultra-fast effect. The early dopamine peak is progressively lost when rats trained to self-administer cocaine are switched to extinction conditions in which they receive saline instead of expected cocaine[48]. The post-response elevation has early and late components (FIG. 1) that can be clearly differentiated in some individual records[47,48] but that vary sufficiently between animals as to be undifferentiated when averaged (for an example, see REF. 47). The late component, with a latency of approximately 3 seconds after the lever-press, is immediately absent when animals are first switched to extinction conditions (FIG. 1); the early component, with latency of approximately 0.5 seconds, is lost only after several extinction trials (FIG. 1). Presumably, this early component disappears only after several extinction trials because it is a response to the exteroceptive cocaine-predictive cues — the earned light and sound cues — that continue to be earned during the extinction trials. The reward-predictive effect of these cues is sustained until the new association with saline is learned. When the association between the earned exteroceptive cues and cocaine has been extinguished (FIG. 1), the early component of the post-response dopamine elevation is also extinguished.

By contrast, the later component of the 5-second post-response dopamine peak (FIG. 1; for example, REF. 48) seems to be lost immediately; it is absent in the very first extinction trials. The immediate loss of the late component suggests that the source of this component (unlike the light and sound cues that continue to be earned) is absent — no longer earned — from the very first extinction trial. The element that is missing from the start of extinction is cocaine (both its central rewarding and its peripheral reward-predicting actions), and we suggest the working hypothesis that a reward-predictive peripheral effect of cocaine is the source of the late component of the ultra-fast dopamine response.

Conclusions and clinical perspective

Cocaine is a powerfully habit-forming drug that continues to pose great problems for individuals and for society despite widespread knowledge of its various adverse consequences. Its addiction liability is largely attributable to the fact that it enters the brain and has rewarding actions with a latency of perhaps tens of seconds.

In experienced cocaine users, cocaine activates the reward system even more quickly. The earliest activation is seen when the drug is self-administered; in this case the dopamine system seems to be initially activated by the intention to take the drug or by the initiation of action to take the drug. Here, the reward system is partially activated a second or two before the drug is actually injected or smoked. Further activation of the reward system occurs when the required response for the drug has been completed. This activation occurs in half a second or so and is a conditioned response to the sights and sounds associated with completion of the response requirement; in the case of the laboratory rat this would be the tactile and auditory consequences of lever-pressing and pump activation (if audible), and any light or sound stimuli that the experimenter has programmed to accompany the injection. Finally, additional activation occurs in response to peripheral actions of cocaine that reliably precede the direct effects of cocaine in the brain. This activation seems to lag slightly behind the activation by exteroceptive cocaine-predictive stimuli, but unlike exteroceptive predictors, the peripheral actions of cocaine are almost certain predictors of the drug's central effects.

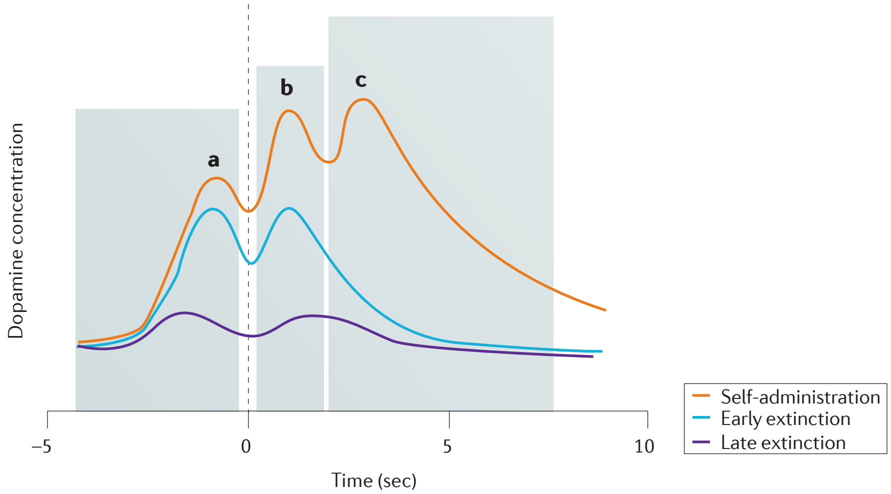

Figure 1 | **Proposed extracellular dopamine fluctuations following cocaine self-administration.** A schematic representation of the proposed components of the extracellular dopamine fluctuations that accompany lever-pressing in intoxicated rats that expect an intravenous cocaine injection. The three idealized peaks are based on selected individual records from fast-scan *in vivo* voltammetry studies[47,48] The elevation before the lever-press (peak **a**) arises as the animal starts to move towards the response lever. Peaks **b** and **c** (the early and late components of this part of the response) are not so clearly differentiated from one another in all animals and tend to overlap in averaged group data. The early portion (0–2 seconds) of the post-response elevation (idealized here as peak **b**; REFS 47,48) is suggested to reflect the response to earned reward predictors, such as the click of the response lever or the illumination of a cue light that accompanies activation of the syringe pump that delivers the drug. This elevation of 0–2 seconds continues to be seen in the early phases of extinction testing, when non-rewarding saline has been substituted for the expected cocaine[48]. This early elevation is progressively lost in late extinction training as the animal forms a new association between the stimuli that once predicted cocaine but now predict saline[48]. The later portion (2–5 seconds) of the post-response elevation (idealized here as peak **c**) is absent in even the early phases of extinction training[48], presumably because it is a response to cocaine-predictive cues that do not continue into extinction training, such as the interoceptive cues of cocaine itself. Figure is modified, with permission, from REF. 48 © (2005) Cell Press.

Thus, whereas the primary, unconditioned rewarding effect of cocaine in naive animals involves the blockade of dopamine reuptake rather than the stimulation of dopamine release, the most immediate rewarding effect of cocaine in cocaine-experienced users is dopamine release triggered as a conditioned response to exteroceptive and interoceptive stimuli that activate the dopamine system trans-synaptically. For this reason, it may be useful to target the peripheral effects of cocaine as a potential target for medication. The effectiveness of vaccines against cocaine — one of the cutting-edge therapies under current study[57–59] — may, in part, be due to the reduction of peripheral cocaine levels.

Conditioned interoceptive effects are also likely to contribute to the effects of other addictive drugs. Indeed, it has been suggested that drug onset cues — presumably peripherally triggered — can cause conditioned opiate withdrawal symptoms[60]. Conditioned interoceptive effects of nicotine may well have a similar role to those of cocaine. Although it has been assumed that nicotine very rapidly reaches high concentration in the brain after each puff of a cigarette, recent evidence suggests that nicotine — even from smoking — accumulates in the brain over minutes rather than seconds[61]. Nicotinic receptors are highly concentrated in the lungs; thus, the peripheral effects of smoked nicotine may, like those of cocaine, be relayed quickly to the brain. Such effects could explain why nicotine is so addictive in humans and much less so in laboratory animals: nicotine is given intravenously in laboratory animals, and its access to peripheral nicotinic receptors is therefore less immediate and more diffuse. Heroin[60] and the amphetamines[62] also have well-known peripheral actions that could signal receipt of the drug before it arrives in the brain and could contribute a conditioned component to the rewarding effects of these drugs in experienced users. Thus, the conditioned interoceptive cues of addictive drugs may play a more important part in addiction than has been widely considered.

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Competing interests statement

The authors declare no competing financial interests.

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