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Why does the rapid delivery of drugs to the brain promote addiction?

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It is widely accepted that the more rapidly drugs of abuse reach the brain the greater their potential for addiction. This might be one reason why cocaine and nicotine are more addictive when they are smoked than when they are administered by other routes. Traditionally, rapidly administered drugs are thought to be more addictive because they are more euphorigenic and/or more reinforcing. However, evidence for this is not compelling. We propose an alternative (although not mutually exclusive) explanation based on the idea that the transition to addiction involves drug-induced plasticity in mesocorticolimbic systems, changes that are manifested behaviourally as psychomotor and incentive sensitization. Recent evidence suggests that rapidly administered cocaine or nicotine preferentially engage mesocorticolimbic circuits, and more readily induce psychomotor sensitization. We conclude that rapidly delivered drugs might promote addiction by promoting forms of neurobehavioural plasticity that contribute to the compulsive pursuit of drugs.

Although many people try potentially addicting drugs, and often do so on more than one occasion, few progress from casual, recreational drug use to the compulsive and excessive patterns of drug taking that characterize addiction. One central question in addiction research, therefore, is what determines whether a given individual undergoes the transition from drug use to drug abuse and addiction. The quest for an answer to this question has generated much research, and it is now known that many factors can facilitate or delay the development of addiction. Most of this research has focused on individual genetic, hormonal and contextual variables [1]. Nevertheless, some characteristics of drugs themselves can influence the progression to addiction. For example, a central dogma in addiction research is that drugs, formulations and routes of administration that result in the rapid entry of a drug into the brain increase the propensity to addiction [2–4]. This might be one reason why, for example, smoked cocaine ('crack') is thought to be more addictive than powdered cocaine taken by insufflation [4], and cigarettes are particularly addictive, whereas products that deliver nicotine slowly are less likely to lead to addiction [5]. Although the potential for addiction is greatest when drugs are administered rapidly, why this occurs is unknown. In this article, we begin with a discussion of two traditional mechanisms by which the rate of drug delivery is thought to influence addiction. We then present new findings that lead us to consider an alternative explanation.

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Why are rapidly administered drugs more addictive?

Greater euphoria?

Two complimentary explanations have been proposed to account for the relationship between the rate of drug delivery and the addictive potential of drugs. The first explanation suggests that rapidly administered drugs promote the transition to addiction because they are more euphorigenic [4,6]. Indeed, ratings of subjective pleasurable effects are more immediate and more intense when addicting drugs are delivered rapidly. For example, self-reports of a 'high', pleasantness and drug-liking are greater when cocaine [7] or heroin [8] are administered intravenously rather than by insufflation, and ratings of euphoria are greater when intravenous infusions of cocaine [9,10] or morphine [11] are delivered rapidly. Similarly, the subjective pleasurable effects of methylphenidate [12] and pentobarbital [13] are greater when these drugs are given in a rapid-onset formulation rather than a slow-onset formulation. Although the effects of dose and rate are confounded in many of these studies, rapidly administered diazepam is reported to produce greater euphoria, 'high', liking and desire for more drug, even when the achieved dose is controlled [6].

Thus, for many drugs there is a positive relationship between the rate of delivery and the subjective experience of euphoria, and this could contribute to some drug addictions in some individuals (although see [14]). However, there might be no necessary causal relationship between the ability of drugs to produce pleasure and their ability to produce addiction [15]. For example, human subjects will self-administer morphine [16] or cocaine [17] at doses that they cannot distinguish from placebo (i.e. doses that produce no subjective effects at all), yet they will not self-administer placebo. Moreover, if drug-seeking were driven primarily by the pursuit of drug-associated pleasure, then the incentive value of drugs in addiction should be proportional to their ability to produce pleasure. However, this might not be the case [15]. As addiction evolves, drugs acquire greater and greater incentive value, and drug-seeking becomes increasingly more fervent, while the pleasurable sensations experienced by addicts generally do not increase. Finally, whereas greater euphoria might contribute to repeated drug use, addiction can develop in

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the absence of strong feelings of euphoria. For example, cigarettes are not particularly euphorigenic, yet they are powerfully addictive. It is true that cigarettes can evoke certain pleasant sensations but generally these do not rival the vividly pleasurable 'rush' or 'state of dreamy indifference' [18] induced by other addicting drugs. These observations have prompted the conclusion that, 'reinforcement mechanisms in tobacco dependence do not appear to depend on intense feelings of subjective pleasure elicited by nicotine' [19]. Thus, it is difficult to maintain that smoking cigarettes is more addictive than using products that deliver nicotine more slowly (e.g. oral moist snuff, Swedish snus, and nicotine replacement products) because smoking produces a greater feeling of elation. It appears, therefore, that although drug pleasure might have a role in modulating drug-taking behaviour, something other than the euphorigenic properties of rapidly administered drugs might contribute to their ability to promote addiction.

Greater reinforcement?

The second explanation suggests that rapidly administered drugs are more addictive because they are more reinforcing. This proposal comes from a limited number of studies showing that increasing the speed of intravenous administration (5–240 s) enhances the ability of cocaine [20–22] and nicotine [23] to support drug self-administration behaviour in monkeys. However, these studies involve a narrow range of doses, a limited range of schedules of reinforcement (either a fixed-ratio schedule of reinforcement, where the performance of a fixed number of operant responses results in a drug infusion, or a fixed-interval schedule of reinforcement, where the performance of an operant response within a fixed time interval results in a drug infusion) and small numbers of experimental subjects. In addition, in the first (but seldom cited) report on the effects of delivery rate on drug reinforcement, Pickens and colleagues [24] concluded that, 'duration of infusion (25–75 s) seems to have little direct importance in controlling either the frequency or the distribution of responding for cocaine reinforcement'. Consistent with the study by Pickens *et al.* [24], we recently found that varying the speed of amphetamine or cocaine delivery between 5 s and 100 s in rats had no effect on: (i) the acquisition of self-administration; (ii) the frequency of responding under two fixed-ratio schedules of reinforcement; (iii) the 'breakpoint' achieved on a progressive ratio schedule of reinforcement (a measure of the amount of effort animals are willing to expend to get a drug infusion); or (iv) on the reinstatement of drug-seeking following extinction of this response [25]. Similarly, using a progressive ratio schedule of reinforcement in male rhesus monkeys, a recent study found that varying the rate of cocaine administration between 10 s and 100 s did not alter its potency or efficacy as a reinforcer, although longer injections (300–600 s) did decrease maximal responding (but still had no effect on potency) [26]. Thus, it appears that the reinforcing effects of psychostimulant drugs might not be influenced by small variations in the rate of drug delivery (i.e. over 5–100 s), although this requires further investigation. Interestingly, variation over this range of infusion rates influences the subjective pleasurable effects of intravenous cocaine administration in humans [10].

The search for an alternative explanation: rate of drug delivery and psychomotor sensitization

If neither an increase in euphoria nor an increase in reinforcing effects fully accounts for why rapidly administered drugs are potentially more addictive, what does? One possibility arises from the idea that addiction is due, at least in part, to the ability of drugs of abuse to reorganize brain regions involved in reward and motivation, such as the dorsal and ventral striatum, and brain regions involved in the inhibitory control of behaviour, such as the prefrontal cortex [15,27–31]. Some of these neuroadaptations are manifested at the level of behaviour by psychomotor and incentive sensitization. Psychomotor sensitization refers to an enduring increase in the psychomotor-activating effects of drugs produced by repeated drug administration. There has been considerable interest in this phenomenon because the neural circuits that underlie these effects are thought to overlap with those that mediate the incentive, motivational effects of drugs [15,29]. It is not surprising, therefore, that repeated exposure to one of several drugs of abuse also produces incentive sensitization, which refers to the process whereby repeated drug exposure renders drugs and cues paired with drug-taking increasingly able to control behaviour [15,29]. For example, animals previously exposed to nicotine, amphetamine or cocaine show: (i) an increased predisposition to self-administer these drugs [32–34]; (ii) an enhanced tendency to approach contexts paired with drug administration [35]; (iii) an increased 'breakpoint' on a progressive ratio schedule of cocaine or amphetamine reinforcement [36]; and (iv) enhanced sensitivity to the motivational impact of Pavlovian conditioned stimuli [37–39]. Similarly, drug-related stimuli also have the capacity to elicit arousal and approach behaviour in humans with a history of drug use [40,41].

These observations have led to the proposal that the drug-induced neuroplastic changes that underlie psychomotor and/or incentive sensitization might contribute to addiction [15,29]. We hypothesized, therefore, that increasing the rate at which addicting drugs are delivered might potentiate their ability to induce behavioural sensitization [42–44]. In a first experiment, the influence of the speed of intravenous cocaine delivery (between 3 s and 100 s) on the development of psychomotor sensitization in rats was examined [42]. Across a range of doses (0.5–2.0 mg kg^{-1}), and using both rotational behaviour observed in rats with a unilateral 6-hydroxydopamine lesion (which destroys nigrostriatal dopamine-containing neurons) and locomotor activity in neurologically intact rats as indices of psychomotor activation, rapid (3–16 s versus 25–100 s) intravenous infusions of cocaine were particularly effective in inducing sensitization [42]. In a more recent study these initial findings were replicated using a single-injection sensitization paradigm in rats [43]. Locomotor sensitization to a single intravenous infusion of cocaine developed when cocaine was delivered rapidly (over 5 s) (Figure 1a) but not when it was delivered

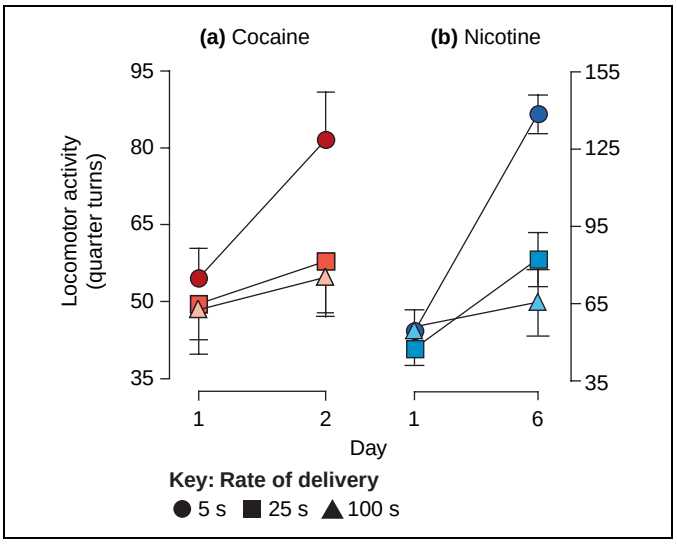

Figure 1. Locomotor activity (quarter turns) following an intravenous infusion of 2.0 mg kg^{-1} cocaine **(a)** or serial infusions (5 infusions per 10 min) of 50 μg kg^{-1} nicotine **(b)** delivered over 5, 25 or 100 s, as a function of the treatment day (values = mean ± SEM). Rapidly administered cocaine and nicotine are particularly effective in producing locomotor sensitization. Adapted from [43] (©2004 Society for Neuroscience) and [44] (©2004 Society of Biological Psychiatry).

more slowly (over 25–100 s). These findings suggest that the rate at which cocaine is delivered influences susceptibility to sensitization. A subsequent study showed that rapid (5 s compared with 25–100 s) intravenous infusions of nicotine also facilitated the development of locomotor sensitization in rats (Figure 1b) [44]. Thus, increasing the rate at which either cocaine or nicotine are administered potentiates their ability to induce behavioural sensitization. The implication, of course, is that the neurobiological impact of cocaine and nicotine must vary as a function of their rate of administration.

The influence of the rate of drug delivery on the neurobiological impact of drugs

Given that it is so widely accepted that the rapid delivery of drugs to the brain promotes addiction, it is surprising that only few studies have examined how the rate of drug delivery influences the neurobiological effects of drugs. The few studies to examine dopamine (DA) activity have not revealed large effects. For example, *in vivo* microdialysis used to quantify DA overflow in the nucleus accumbens of rats following intravenous infusions of a fixed dose of cocaine delivered over 6 s or 150 s showed that maximal levels of cocaine-induced DA overflow were the same in the two conditions, although the rate of rise of DA levels was greater following the faster infusion [45] (also see [46]). The influence of the cocaine infusion rate (10, 300 or 600 s) on the temporal dynamics of *in vivo* DA transporter binding in the striatum of rats has also been examined [26]. Maximum transporter occupancy did not differ over the range of infusion rates studied but maximum blockade was attained earlier following faster infusions [26]. These observations are reminiscent of a study showing that, in humans, the levels of DA transporter blockade are comparable following intranasal, intravenous and smoked cocaine [47]. However, for equivalent levels of cocaine in plasma and DA transporter occupancy, smoked cocaine leads to greater self-reports of a 'high' than does intranasally administered cocaine [47]. The influence of the rate of intravenous cocaine administration (5–100 s) on the half-life of electrically evoked DA release in the nucleus accumbens core was examined recently in rats using *in vivo* voltammetry [43]. As expected, the kinetics of the cocaine-induced increase in the half-life of DA were influenced by the rate of infusion but rapid infusions also produced a greater maximum increase in the half-life of DA, although this effect was relatively small and short-lasting (3–4 min) [43]. Thus, varying the rate of cocaine delivery, at least over 5–100 s, alters the kinetics of the DA response but has only a relatively modest effect on the magnitude of this response. It is also interesting to note that estimation in rats of the temporal dynamics of cocaine delivery to the brain over 5–100 s indicated that the maximal brain concentrations of cocaine should not differ under these conditions [42].

The rate of drug delivery influences which cells and circuits are engaged by cocaine and nicotine

Although measures of DA dynamics have not revealed large effects of the rate of cocaine delivery, there is evidence to suggest that the rate of drug delivery alters the neurobiological impact of drugs. One study [48] examined the influence of the route of cocaine administration on glucose utilization in the brains of rats. Over a wide range of doses, intraperitoneal administration of cocaine induced metabolic changes primarily in structures related to nigrostriatal circuitry, such as the substantia nigra pars reticulata and globus pallidus, but failed to change glucose utilization in components of the mesocorticolimbic system. By contrast, intravenous administration of cocaine increased glucose utilization not only in the nigrostriatal system, but also in the medial prefrontal cortex (mPFC), nucleus accumbens, olfactory tubercle and lateral habenula. The author concluded that, 'cocaine activates different neuronal circuitry depending on the route by which it is administered', and that this difference was most probably the result of pharmacokinetic factors (i.e. rate of drug delivery) and not dose-related factors [48].

These findings prompted the question of how varying the rate at which drugs of abuse are delivered to the brain, while keeping the route of administration constant, would influence cellular activity within specific neural circuits. Immediate early genes (IEGs) are induced rapidly in response to a variety of stimuli, including drugs of abuse, and reflect the biochemical activation of signal-transduction pathways [49,50]. In addition, the initial phases of drug experience-dependent plasticity, such as sensitization, involve activation of IEGs [27,28]. Therefore, the IEGs c-*Fos* and *Arc* were used to visualize the cells and circuits engaged by an intravenous infusion of either cocaine or nicotine as a function of delivery rate (5–100 s). The rapid delivery of cocaine [43] or nicotine [44] to rats potentiated their ability to induce c-*Fos* and *Arc* mRNA expression, particularly in mesocorticolimbic regions such as the mPFC, the nucleus accumbens and the caudate–putamen (also known as the dorsal striatum in rats) (Figures 2–4). Interestingly, the dose of cocaine studied (2 mg kg^{-1}) increased gene expression in the mPFC only

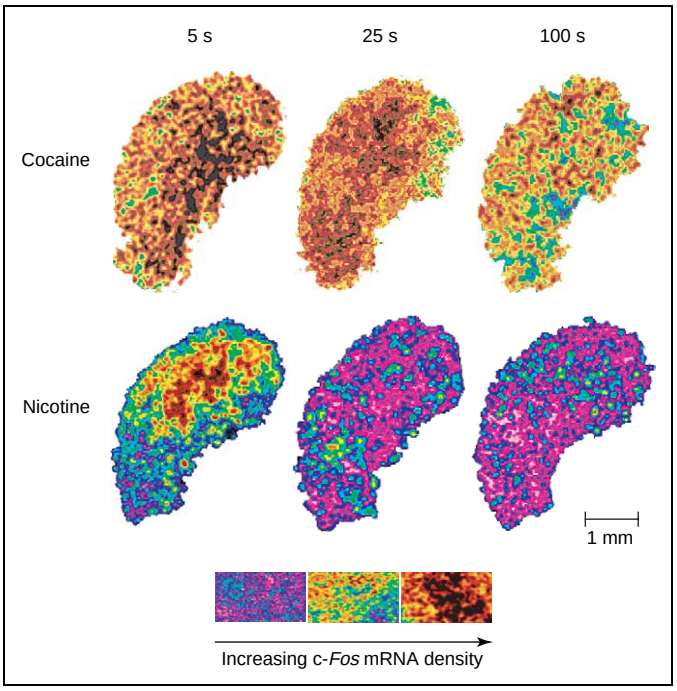

Figure 2. Representative densitograms illustrating the expression of mRNA for the immediate early gene c-*Fos* in the caudate–putamen of rats given intravenous cocaine (top) or nicotine (bottom) over 5, 25 or 100 s. Note that tissue from animals treated with cocaine was processed separately from that of animals treated with nicotine. For this reason, it might not be suitable to compare c-*Fos* mRNA density across drugs. Increasing the rate at which cocaine or nicotine are delivered potentiates their ability to alter gene regulation in the caudate–putamen. Adapted from [43] (©2004 Society for Neuroscience) and [44] (©2004 Society of Biological Psychiatry).

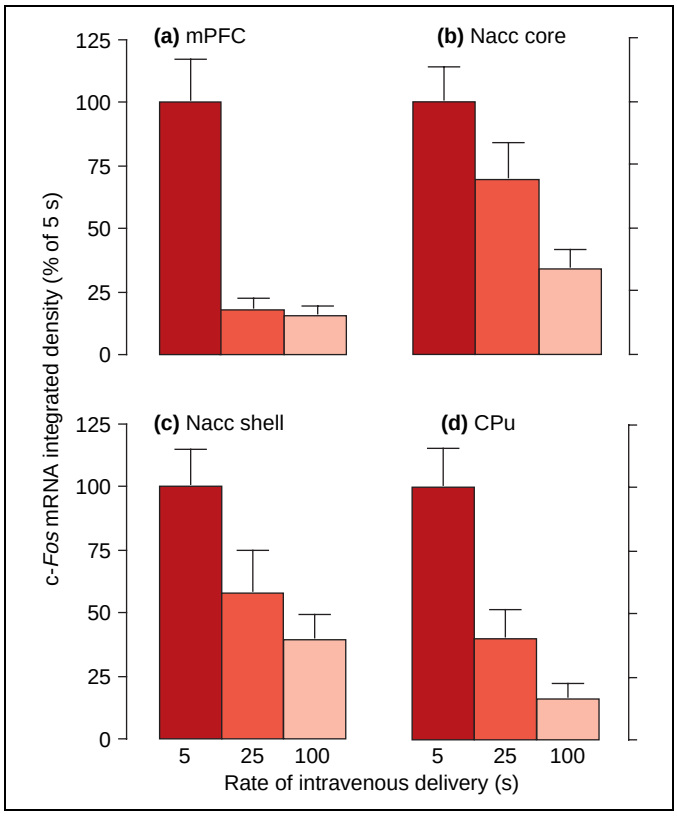

Figure 3. Cocaine-induced c-*Fos* mRNA expression (depicted as percentage of that in rats given cocaine over 5 s) in **(a)** the medial prefrontal cortex (mPFC), **(b)** the nucleus accumbens (Nacc) core, **(c)** the Nacc shell and **(d)** the caudate–putamen (CPu) as a function of the intravenous delivery rate (values = mean% 5 s ± SEM). Integrated density values following an infusion of saline were between 0.2% and 7.8% of those seen following an infusion of cocaine over 5 s (data not shown). Rapidly delivered cocaine preferentially engages mesocorticolimbic structures. Adapted from [43] (©2004 Society for Neuroscience).

when it was administered rapidly (Figure 3a) [43]. The mPFC serves several complex executive functions, including the regulation of motivational impulses, attention and decision-making [30,51]. The mPFC is also required for the development of behavioural sensitization [52,53], and is implicated in relapse to drug-seeking following the extinction of self-administration [54].

The rate of drug delivery also determined the phenotype of cells engaged by cocaine and nicotine. For example, the caudate–putamen contains two major subpopulations of projection neurons. One population preferentially expresses mRNA for the neuropeptide preproenkephalin (i.e. Enk+ cells) and forms the striatopallidal pathway (i.e. projects from the striatum to the globus pallidus), whereas the other population does not express preproenkephalin mRNA (i.e. Enk− cells) and forms the striatonigral pathway (i.e. projects from the striatum to the substantia nigra) [55]. Conditions that facilitate the development of behavioural sensitization (e.g. pairing psychostimulant administration with a novel environment) also facilitate drug-induced gene expression in Enk+ cells within the caudate–putamen [56,57]. Consistent with these reports, cocaine [43] and nicotine [44] did not significantly increase c-*Fos* expression in Enk+ cells when administered more slowly (25–100 s). When given over 5 s, however, these drugs did increase c-*Fos* expression in Enk+ cells.

The ability of cocaine to block DA reuptake and thereby enhance DA-mediated neurotransmission is thought to underlie its effects on IEG expression [58]. This leads us to consider two possibilities. First, the effect of the rate of cocaine administration on IEG expression is mediated primarily through its effects on DA. If this is true, then it follows that small and brief differences in extracellular DA levels (at least as estimated by the change in the half-life of DA) [43] must lead to relatively large differences in gene expression in postsynaptic cells. Second, the effect of the rate of drug infusion on gene expression additionally involves non-DA-mediated mechanisms (e.g. glutamate), a hypothesis that remains to be explored.

Concluding remarks

These findings demonstrate that differences in the rate at which addicting drugs are administered determine their ability to produce psychomotor sensitization, and presumably its associated adaptations in the brain. These results represent a first step in characterizing an as yet unknown and unappreciated relationship between the rate of drug delivery and the ability of addicting drugs to produce forms of neurobehavioural plasticity that might lead to excessive incentive motivation for drugs (i.e. sensitization). What is truly remarkable is that a difference of 20 s in the rate of cocaine or nicotine delivery is sufficient to determine whether persistent changes in behaviour occur and whether specific neural circuits are engaged. A future challenge for neurobiology is to

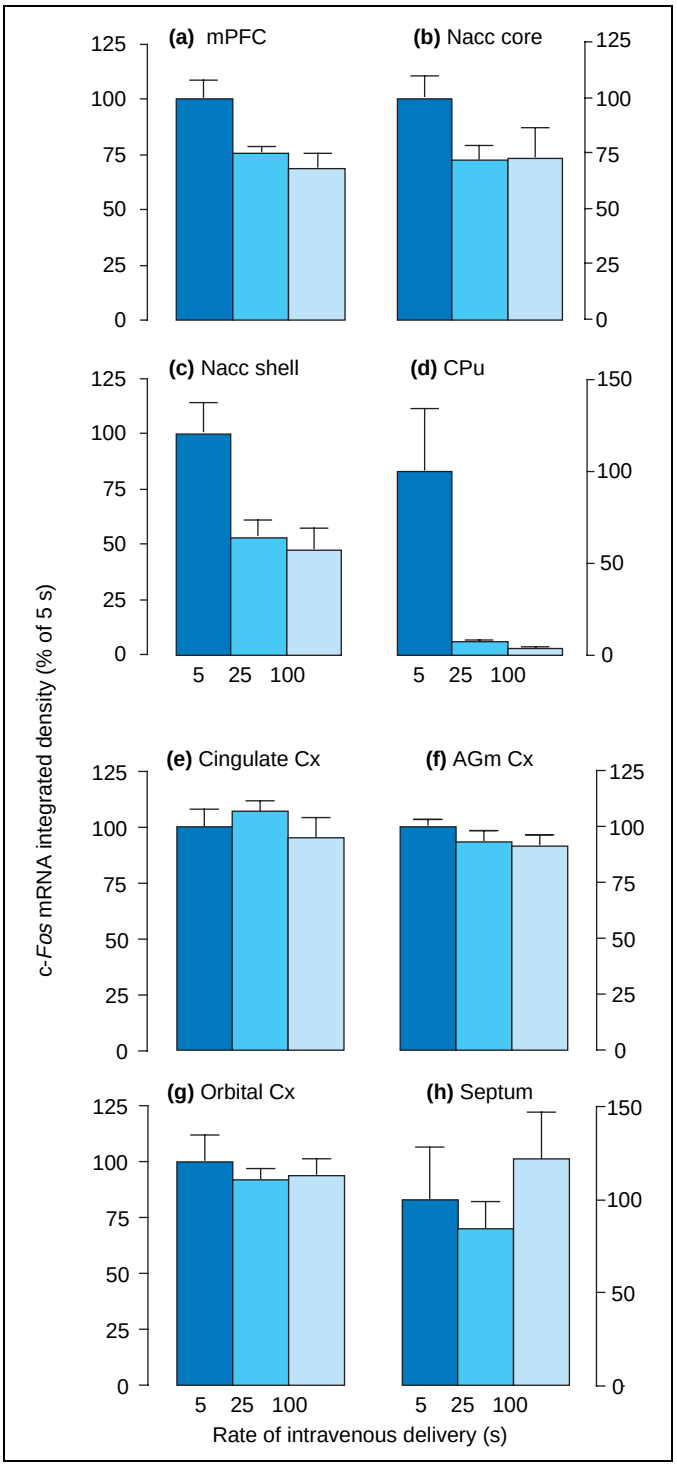

Figure 4. Nicotine-induced c-*Fos* mRNA expression (depicted as percentage of that in rats given nicotine over 5 s) in brain regions where there was an effect of the rate of intravenous drug infusion [**(a)** medial prefrontal cortex (mPFC), **(b)** nucleus accumbens (Nacc) core, **(c)** Nacc shell and **(d)** dorsal caudate–putamen (CPu)] and brain regions where there was no effect [**(e)** cingulate cortex (Cx), **(f)** medial agranular (AGm) cortex, **(g)** lateral orbital cortex and **(h)** septum] as a function of the intravenous delivery rate. Integrated density values following an infusion of saline were between 5.1% and 26% of those seen following an infusion of nicotine over 5 s (data not shown). Increasing the rate of nicotine delivery promotes its ability to induce immediate early gene (IEG) expression, particularly in mesocorticolimbic regions. Adapted from [44] (©2004 Society of Biological Psychiatry).

determine the mechanisms by which differences in the temporal dynamics of cellular activation produce differences in the recruitment of intracellular signaling cascades, and subsequent plasticity.

Whatever the mechanisms might be, the behavioural results clearly indicate that the neuroadaptive processes initiated by addictive drugs are sensitive to the rate of drug administration. Thus, we hypothesize that the reason drugs, formulations and routes of administration that result in the rapid delivery of drugs to the brain preferentially promote the transition to addiction is not simply because this makes drugs more euphorigenic or reinforcing but because this facilitates their ability to induce forms of neurobehavioural plasticity that contribute to compulsive and excessive drug use.

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