

Brain Reward Circuitry: Insights from Unsensed Incentives

Review

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The natural incentives that shape behavior reach the central circuitry of motivation trans-synaptically, via the five senses, whereas the laboratory rewards of intracranial stimulation or drug injections activate reward circuitry directly, bypassing peripheral sensory pathways. The unsensed incentives of brain stimulation and intracranial drug injections thus give us tools to identify reward circuit elements within the associational portions of the CNS. Such studies have implicated the mesolimbic dopamine system and several of its afferents and efferents in motivational function. Comparisons of natural and laboratory incentives suggest hypotheses as to why some habits become compulsive and give insights into the roles of reinforcement and of prediction of reinforcement in habit formation.

The discovery by Olds and Milner (1954) that rats would learn to work for direct electrical stimulation of the brain initiated the search for the anatomical circuitry through which the normal pleasures of life establish habits that come to dominate the behavior of higher animals. It soon became apparent that lateral hypothalamic brain stimulation was not only rewarding; it was also drive inducing (Olds and Olds, 1965; Coons et al., 1965; Glickman and Schiff, 1967). Electrical stimulation of reward-related structures thus became a tool to identify anatomical substrates presumed to participate in natural motivation (Mendelson and Chorover, 1965; MacDonnell and Flynn, 1966a, 1966b; Wise, 1974) and reward (Olds and Olds, 1963; German and Bowden, 1974; Routtenberg, 1976). Inasmuch as the reward of direct brain stimulation was not detected by sight, sound, taste, smell, or touch, it provided an unsensed incentive with some degree of anatomical specificity. Intravenous (Weeks, 1962; Thompson and Schuster, 1964; Deneau et al., 1969) and intracranial (Olds et al., 1964; Phillips and LePiane, 1980; Bozarth and Wise, 1981) drug reinforcement soon offered an unsensed incentive with neurochemical specificity. These two techniques have subsequently been used extensively to characterize brain reward circuitry with respect to both its anatomy and neurochemistry. Because these laboratory incentives are not detected in the external world of the animal, they also reveal important insights into behavior motivated by natural rewards. The present paper comprises three sections. The first characterizes the elements of brain reward circuitry that have been identified by central drug injections and intracranial stimulation and that offer our best clues

as to the trigger zones at which addictive drugs initiate their habit-forming actions. The second discusses possible explanations for the fact that drug reward and brain stimulation reward establish seemingly more compulsive habits than do the natural pleasures of life. The final section illustrates—again, by contrasting sensed and unsensed incentives—the fuzziness of the distinction between the “receipt” of reward and the prediction of reward.

Anatomy of Drug Reward

While there is much to learn about which dopamine neurons play roles in incentive motivation and reinforcement and there is much more to learn about the afferents to and the efferents from those dopamine neurons, a good deal is known about the brain structures and receptor subtypes at which addictive drugs trigger their habit-forming actions. This information comes in large part from studies involving intracranial drug injections that are reviewed below. The guiding assumption of such studies is that the relevant receptors for drug reward are to be found at sites where the lowest doses of microinjected drugs are rewarding. This is a fair assumption so long as care is taken to sample enough injection sites to ensure that the site of action is at the site of microinjection. The minimum controls for ensuring the validity of this assumption are “geologic” controls; unless one can demonstrate that similar injections in the regions bounding the putative site of action are *not* rewarding, one can never be sure that the drug is not spreading to act at a distance (Routtenberg, 1972; Wise and Hoffman, 1992). Of particular danger with hydraulic injections is that the drug spreads up the cannula shaft to a distant site of action or to the ventricular system (a pressure sink that is frequently penetrated by injection cannulae). The dangers of such spread are well illustrated by studies of the dipsogenic actions of carbachol (Routtenberg and Simpson, 1974) and angiotensin (Johnson and Epstein, 1975).

The Mesolimbic Dopamine System

A number of drugs are rewarding when injected into the nucleus accumbens where they act at mesolimbic dopamine terminals. Amphetamine, a dopamine releaser, is self-administered (Hoebel et al., 1983) and establishes conditioned place preferences (Carr and White, 1983) when injected into this region. Amphetamine injections into this region also potentiate (summate with) the rewarding effects of lateral hypothalamic brain stimulation (Colle and Wise, 1988). The dopamine uptake inhibitors nomifensine and cocaine are also self-administered into nucleus accumbens; injections into the shell are effective, whereas injections into the more dorsal and lateral core are not (Carlezon et al., 1995). Nomifensine also potentiates lateral hypothalamic brain stimulation reward by its action in this region (Carlezon and Wise, 1996b).

Cholinergic agents are rewarding when injected into the ventral tegmental area (VTA). Cytisine, a nicotinic agonist, induces conditioned place preference when in-

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jected into the VTA but not when injected just dorsal to it (Museo and Wise, 1994). The cholinergic agonist carbachol causes conditioned place preference when injected into the VTA (Yeomans et al., 1985). Carbachol and the acetylcholinesterase inhibitor neostigmine are self-administered into the VTA; posterior VTA injections are most effective, and injections dorsal or lateral to the VTA are ineffective (Ikemoto and Wise, 2002). Low doses of carbachol are effective in producing conditioned place preferences when injected into the posterior but not the anterior VTA and not dorsal to the posterior VTA (Ikemoto and Wise, 2002). Carbachol activates both muscarinic and nicotinic receptors, and each type of receptor is expressed by dopaminergic neurons (Clarke and Pert, 1985; Weiner et al., 1990) and appears to contribute to carbachol's rewarding (Ikemoto and Wise, 2002) and reward-enhancing (Yeomans and Baptista, 1997) effects in this region.

Rewarding hypothalamic brain stimulation appears to depend on trans-synaptically induced release of acetylcholine in the VTA (Yeomans et al., 1985). The axons of the mesolimbic dopamine system have high thresholds, and very few are directly activated, at traditional stimulation parameters, by rewarding hypothalamic stimulation (Yeomans, 1989; Murray and Shizgal, 1994). The bulk of the "first-stage" hypothalamic reward fibers—the reward-relevant portion of the medial forebrain bundle that is directly depolarized by cathodal current in the lateral hypothalamic medial forebrain bundle—are thought to be caudally projecting fibers (Bielajew and Shizgal, 1986) with refractory periods in the range of 0.4–2.5 ms (Yeomans, 1979; Bielajew et al., 1982; Gratton and Wise, 1985) and conduction velocities in the range of 2–8 m/s (Bielajew and Shizgal, 1982; Murray and Shizgal, 1994). At least the major portion of these fibers is thought to synapse in the pedunculopontine or latero-dorsal tegmental nucleus, the cholinergic efferents of which relay their message back to the VTA (Yeomans et al., 1993). Hypothalamic brain stimulation reward elevates acetylcholine levels in the VTA (Rada et al., 2000), where injections of muscarinic blockers elevate reward thresholds (Yeomans et al., 1985; Kofman et al., 1990; Yeomans and Baptista, 1997). Conversely, VTA injections of acetylcholine decrease the threshold for hypothalamic brain stimulation reward (Redgrave and Horrell, 1976). The VTA cholinergic contribution to brain stimulation reward appears to involve the activation of the mesolimbic dopamine system at M5 muscarinic receptors expressed by the dopaminergic neurons of this region (Yeomans et al., 2000, 2001; Forster et al., 2002)

Mesolimbic Afferents

Opiates appear to have their strongest rewarding effects through afferents to the mesolimbic dopamine system. Mu and delta opioids are self-administered into the region of the mesolimbic dopamine cell bodies of the VTA (Bozarth and Wise, 1981; Welzl et al., 1989; Devine and Wise, 1994; David et al., 2002). The selective mu agonist DAMGO is effective at two orders of magnitude lower doses than the selective delta agonist DPDPE (Devine and Wise, 1994); the two activate the mesolimbic dopamine system with the same relative potencies (Devine et al., 1993). The presumed mechanism of action of mu opioids in this region involves disinhibition of the dopamine system by inhibition of nearby GABAergic

neurons that normally hold their dopaminergic neighbors under inhibitory control (Johnson and North, 1992).

GABAergic agents themselves are also self-administered into the VTA (Ikemoto et al., 1997c, 1998b; David et al., 1997). The GABA_A antagonists picrotoxin and bicuculline are self-administered into the anterior VTA, while, somewhat surprisingly, the GABA_A agonist muscimol is self-administered into the posterior VTA; co-infusion of muscimol antagonizes the rewarding effects of anterior VTA picrotoxin injections, and, conversely, co-infusion of picrotoxin antagonizes the rewarding effects of posterior VTA muscimol injections. Self-administration of the GABA_A antagonists, at least, is thought to be dopamine dependent (Ikemoto et al., 1997b; David et al., 1997). The mechanisms for these effects are not yet completely clear, because GABA_A receptors are expressed not only by VTA dopamine neurons (Sugita et al., 1992) but also by the GABAergic neurons that normally inhibit the dopamine neurons (Rick and Lacey, 1994).

Microinjections of dopamine D1 antagonists in the VTA attenuate the rewarding effects of intravenous cocaine (Ranaldi and Wise, 2001), presumably by blocking the effects of dendritically released dopamine on either GABAergic (Starr, 1987; Cameron and Williams, 1993) or glutamatergic (Kalivas and Duffy, 1995) inputs to the region. Glutamatergic input to the VTA appears to offer an important link in the brain's reward circuitry. VTA glutamate inputs arise from cortical sites including the frontal cortex. Rats will lever-press for injections of phencyclidine and other NMDA antagonists into the frontal cortex (Carlezon and Wise, 1996a), and direct electrical stimulation in this region is also rewarding (Routtenberg and Sloan, 1972; Corbett et al., 1985). Such stimulation causes glutamate release in the VTA; blockade of ionotropic glutamate receptors in VTA blocks the rewarding effects of such stimulation as well as the ability of such stimulation to elevate nucleus accumbens dopamine levels (You et al., 1998).

Mesolimbic Efferents

The mesolimbic dopamine system synapses on the shafts of the dendritic spines of GABA-containing medium spiny neurons of nucleus accumbens (Bouyer et al., 1984). The medium spiny neurons express both D1-type and D2-type dopamine receptors (Surmeier et al., 1996), though the D1-type receptors are largely restricted to a subpopulation of medium spiny neurons expressing dynorphin and substance P and projecting to the zona reticulata of the substantia nigra, whereas the D2-type receptors are largely restricted to a subpopulation of medium spiny neurons expressing enkephalin and projecting primarily to the pallidum (Gerfen, 1992). A third subpopulation of medium spiny neurons co-expresses substance P and enkephalin and similarly co-expresses both D1-type and D2-type dopamine receptors (Surmeier et al., 1996; Aizman et al., 2000); the projection of this subpopulation is not known. Rats do not self-administer either selective D1 or D2 agonists by themselves but do self-administer a mixture of the two (Ikemoto et al., 1997a). It is tempting to suppose that they self-administer the mixture because of its actions on the subpopulation expressing both receptor subtypes, but most behavioral effects of dopaminergic agonists require cooperativity between the two receptor subtypes (Woolverton, 1986; Walters et al., 1987; Clark and

White, 1987), and it is not clear that all such effects depend on only the subpopulation expressing both receptors.

Glutamatergic inputs from a variety of cortical sources synapse on the heads of medium spiny neurons in nucleus accumbens, and antagonists of the NMDA-type glutamate receptor are self-administered into this region. The rewarding effects of phencyclidine and other NMDA antagonists are localized to the nucleus accumbens shell; injections in the core are not effective (Carlezon and Wise, 1996a). Unlike the rewarding effects of the dopamine uptake inhibitor nomifensine and despite the fact that phencyclidine is, like nomifensine (but at higher concentrations), a dopamine uptake inhibitor (Gerhardt et al., 1987), the effects of self-administered doses of nucleus accumbens phencyclidine and other NMDA antagonists are not antagonized by dopamine receptor blockers (Carlezon and Wise, 1996a). Nucleus accumbens injections of phencyclidine and other NMDA antagonists also potentiate lateral hypothalamic brain stimulation reward (Carlezon and Wise, 1996b).

Opiates, too, are self-administered into nucleus accumbens. Morphine (Olds, 1982; David and Cazala, 2000) and the mixed mu-delta agonist methionine enkephalin (Goeders et al., 1984) are each effective, while the selective mu agonist endomorphin-1 is not (Zangen et al., 2002). While opiates in nucleus accumbens induce locomotion, their dopamine-independent actions in nucleus accumbens require an order of magnitude higher doses than do their dopamine-dependent actions in the ventral tegmental area (Kalivas et al., 1983). Interestingly, the locomotor stimulant effects of opioids in nucleus accumbens are enhanced by treatments that cause dopamine depletion or block dopamine receptor function in this region (Stinus et al., 1985, 1986).

Finally, rats self-administer the cholinergic agonist carbachol into nucleus accumbens (Ikemoto et al., 1998a). Cholinergic interneurons are sparse in this region (they comprise less than 2% of all striatal neurons), but they branch profusely and innervate the medium spiny neurons of this region (Walaas and Fonnum, 1979; Phelps et al., 1985).

The medium spiny neurons of nucleus accumbens are the output neurons of this region; they may be viewed as a final common path for the currently identified portions of drug reward circuitry. It would appear to be depression of medium spiny neuron output—direct inhibition in the case of dopamine agonists or opiates and inhibition of excitatory input in the case of NMDA antagonists—that is common to these various drug rewards. It is not clear whether all or merely a subset of medium spiny neurons contributes to reward function.

Reward and Compulsion

The defining property of rewards or “reinforcers” is that they “stamp in” (Thorndike, 1898) learned associations (Pavlov, 1928) and response habits (Thorndike 1898, 1933; Skinner, 1933). The distinction between a habit and an addiction has never been a clean distinction (West, 1992; Robinson and Pritchard, 1995; Stolerman and Jarvis, 1995). With the failure of traditional dependence theory to provide a definition of addiction that covers the cases of stimulants like cocaine and nicotine

(Jaffe, 1985; Wise, 1988), the current distinction between a habit and an addiction is that an addiction is a *compulsive* habit maintained despite harmful consequences (Jaffe, 1985; Leshner, 1999; McLellan et al., 2000). Inasmuch as it is as difficult to objectively define compulsion as it is to define addiction, the distinction between a simple habit and a compulsive habit seems more likely to be a quantitative than a qualitative distinction. Nonetheless, the attempt to characterize the mechanisms responsible for the transition from a simple habit to a compulsive habit has led to a major thrust of current work on addiction: the search for neuroadaptations that can explain the transition from habit to compulsion (e.g., Nestler, 1992, 2001; Robinson and Berridge, 1993, 2000; White and Kalivas, 1998; Berke and Hyman, 2000; Laakso et al., 2002 [this issue of *Neuron*]). The unsensed incentives of brain stimulation and intravenous drugs establish self-administration habits sufficiently compulsive as to qualify as addictions and offer potential insights into the neuroadaptations involved in reinforcement and addiction.

Unsensed incentives can establish very compulsive habits of seeking and ingesting. Rats will work continuously—lever-pressing at rates of several thousand responses per hour—for days to obtain direct electrical stimulation of the lateral hypothalamus and related brain regions (Olds, 1958b; Annau et al., 1974). They do so to the exclusion of other behaviors, starving themselves for the opportunity to self-stimulate if food and stimulation are concurrently available for only a limited portion of each day (Routtenberg and Lindy, 1965). Once experienced with the stimulation, rats will cross electrified grids to gain access to the lever, accepting higher shock to obtain stimulation than they are willing to accept to obtain food (even when deprived for 24 hr [Olds, 1959]). The most obvious hypotheses as to why brain stimulation reward is so effective are (1) that they activate the reward pathway directly, bypassing synaptic barriers in sensory pathways (Wise, 1987); (2) that they activate the reward pathway powerfully, directly depolarizing a population of reward fibers within a radius of 0.25–0.5 mm (Fouriez and Wise, 1984); and (3) that they do so with no delay of reinforcement (even a delay of 1 s between the lever-press and the delivery of reward can dramatically reduce reward effectiveness [Black et al., 1985; Fouriez and Randall, 1997]). Rats and monkeys will work similarly compulsively for intravenous stimulants; if given unlimited access, they will self-administer intravenous injections of these drugs to the point of severe weight loss and death (Johanson et al., 1976; Bozarth and Wise, 1985). What begins as a tentative response tendency becomes a compulsive habit very quickly.

In the case of brain stimulation reward, the habit of self-administration appears to become compulsive almost immediately. The first few lever-presses that result in lateral or posterior hypothalamic stimulation are, of course, accidental. However, rats begin to respond in a focused and frenetic fashion after as few as two or three earned stimulations (Olds, 1958a). That the behavior is locked in so quickly raises serious questions as to whether any of the known neuroadaptations associated with addiction (see, for example, Nestler, 1992, 2001; Robinson and Berridge, 1993, 2000; White and Kalivas,

1998; Berke and Hyman, 2000; Hyman and Malenka, 2001)—above and beyond the neuroadaptations involved in laying down a memory trace for past drug experience—could be a necessary condition for the development of a compulsive habit from a simple habit.

In the case of self-administration of intravenous stimulants or opiates, the compulsive nature of the early response habit is less dramatic. Rats appear to pursue intravenous heroin compulsively after as little as a single earned injection, but they tend to respond at rates of only two or three responses per hour because of apparent satiety (Wise et al., 1995a). Unlike brain stimulation reward, which is usually terminated abruptly 200–500 ms after its onset, drug reward decays slowly, usually by first-order kinetics. (When trains of rewarding brain stimulation reward are delivered with the slow rise and decay times of rewarding drug injections, brain stimulation, too, produces periods of satiety [Lepore and Franklin, 1992]). While animals frequently learn to respond for intravenous cocaine in the first hour or two of opportunity, the development of compulsive responding is less rapid with this drug than with heroin. Short-latency repetition of the instrumental task is infrequent in the early days of training. For example, a typical case involved an animal that responded for 1 mg/kg injections at intervals of between 14 and 55 min in the first 4 hr session. In the second session, the animal began responding more regularly, with inter-response intervals of 6–13 min after three longer latencies at the beginning of the session. By the fourth day, the animal was responding at 6 ± 2 min intervals. This degree of regularity of responding is itself an indication of compulsive behavior and is sufficient to allow confident prediction that if unlimited drug access is continued the animal will self-administer it to the point of self-induced starvation and death (Bozarth and Wise, 1985). Thus, where compulsiveness is demonstrated in tens of seconds by animals lever-pressing for brain stimulation reward and in tens of minutes in animals lever-pressing for intravenous heroin reward, it is demonstrated more on the order of days with intravenous cocaine or amphetamine self-administration. Nonetheless, one must wonder, even with cocaine and amphetamine reward, how much neuroadaptation could have taken place before the habit was stamped in to the point of compulsion.

The classic explanation for addiction is, first, that initial “recreational” use of a drug causes compensatory physiological adaptations to the drug that render the addicted brain different from the non-addicted brain and that require the user to escalate intake in order to maintain the desired effect of the drug. In this view, the neuroadaptations are thought to explain the transition from recreational to compulsive drug use. From this perspective, it should not be necessary for the animal to self-administer the drug in order to develop the adaptations that establish compulsion. Rather, compulsive self-administration should develop quickly after sufficient pre-exposure to induce the hypothesized adaptations. This prediction does not stand up very well against the facts. For example, there have been countless failed attempts to establish compulsive alcohol consumption in rodents by first establishing alcohol dependence (Lester, 1966; Falk et al., 1972; Mello, 1973; Cicero, 1980). Some success seems possible if extreme measures are

taken, but it appears that alcohol must be established as a reinforcer *before* dependence is induced if dependence is to augment intake in such cases (Roberts et al., 2000). Opiate dependence, too, seems not a sufficient condition for establishing compulsive opiate self-administration: it has been estimated that fewer than 0.01% of patients receiving chronic opiates passively are at risk for subsequent addiction (Woods, 1990). Finally, addiction involves compulsive *habits* of drug self-administration. Subjects receiving drug passively do not build up the motor memories for the skilled acts of the drug-taking ritual or the procedures of drug procurement. It is the ex-user returning on the train to the place where he or she has self-administered the drug, not the ex-patient returning on the train to the hospital where he or she was treated, that experiences drug cravings and conditioned withdrawal symptoms (O'Brien et al., 1998).

Early addiction theories focused on autonomic withdrawal symptoms as evidence for the critical physiological adaptations that were the basis of compulsive drug taking; these symptoms are now known not to be necessary for compulsive drug seeking (Deneau et al., 1969; Woods and Schuster, 1971; Bozarth and Wise, 1984; Woods, 1990). Current attention focuses instead on neuroadaptations within the brain circuitry of reward itself (Koob and Bloom, 1988; Nestler, 1992; White and Kalivas, 1998; Berke and Hyman, 2000; Nestler, 2001). Neuroadaptations within the reward circuitry, though having no overt signs, could alter drug responsiveness and thus alter drug intake. This notion is supported by findings that thresholds for brain stimulation reward are higher in animals withdrawn from various drugs of abuse (Leith and Barrett, 1976; Kokkinidis et al., 1980; Kokkinidis and McCarter, 1990; Frank et al., 1988; Schulteis et al., 1995; Watkins et al., 2000). While animals that are allowed to earn moderate doses of intravenous drugs for short periods each day tend to regulate their drug intake (Pickens and Thompson, 1968; Gerber and Wise, 1989; Wise et al., 1995a, 1995b; Ranaldi et al., 1999), animals that are given access to high doses for long periods can show escalation (Ahmed and Koob, 1998) and dysregulation (Tornatzky and Miczek, 2000) of intake. One hypothesis is that prolonged high doses destabilize the mechanisms by which animals regulate limited-access drug intake (Koob and Le Moal, 2001) and that when pushed too far they, like other stress mechanisms (Sterling and Eyer, 1988; Schulkin et al., 1994), never return fully to normal. The clearest correlate of drug satiety is dopamine level in nucleus accumbens (Wise et al., 1995a, 1995b; Ranaldi and Wise, 2001).

Animals that are given repeated intermittent experimenter-administered doses of opiates or psychomotor stimulants become sensitized to these drugs, showing increased responsiveness to their locomotor stimulating (Downs and Eddy, 1932; Segal and Mandell, 1974; Bartoletti et al., 1983; Kalivas and Duffy, 1987) and rewarding (Lett, 1989; Piazza et al., 1990; Horger et al., 1990; Shippenberg and Heidbreder, 1995; Vezina et al., 1999) effects. This sensitization is long lasting and appears to involve enhanced responsiveness of the mesolimbic dopamine system or its synaptic targets (Wolf et al., 1993; Paulson and Robinson, 1995; Heidbreder et al., 1996; Nestler, 2001). Just as desensitization or tolerance of the reward circuitry has been offered as an explanation

of escalating and compulsive drug seeking (Koob, 1996), so has its opposite, sensitization or “reverse-tolerance,” been suggested to underlie the compulsive drug seeking of addiction (Robinson and Berridge, 2000).

While it is clearly the case that brain changes associated with tolerance and dependence and brain changes associated with sensitization can develop under the right circumstances, what remains to be determined is the degree to which either of these changes is necessary for motivational habits to become compulsive. The rapid onset of compulsive self-stimulation would seem to preclude any of these drug-induced long-term neuroadaptations as a necessary condition for compulsive drug seeking. Indeed, given the strong dosing regimens that have been used to demonstrate reliable neuroadaptations, one might ask the opposite question: is, perhaps, compulsive drug seeking a necessary precursor for the development of neuroadaptations in animals not subjected to experimenter-administered drugs? Similarly, one might ask if other motivational compulsions, such as compulsive eating, compulsive sexual activity, or compulsive gambling, are likely to affect the nervous system strongly enough to produce any of the neuroadaptations associated with drugs of abuse. One direction that is just beginning to be explored is whether any of the known neuroadaptations can be established with the minimal drug treatments necessary before drug self-administration becomes compulsive or, for that matter, before animals become behaviorally sensitized to the drugs. A second fact that is just beginning to receive attention is that increases in the tendency for compulsive drug-seeking behavior can grow in the absence of drug-seeking opportunity; indeed, drug seeking can be many times stronger a few weeks (Shalev et al., 2001) or a few months (Grimm et al., 2001) after the last exposure to drug. A third interesting direction is the study of the effects of drug exposure on other motivated behaviors (Mitchell and Stewart, 1990; Harmer and Phillips, 1998; Fiorino and Phillips, 1999; Taylor and Horger, 1999). While sensed incentives may not activate the brain strongly enough to sensitize it to drugs, drug incentives may activate it strongly enough to sensitize the brain to more natural (and modest) sensed incentives.

The alternative to the view that drug-induced neuroadaptations make drug-seeking compulsive is that the neuroadaptations that differentiate the addicted from the non-addicted brain are the neuroadaptations associated with the learning of the drug-seeking habit. The memory of early drug experiences are stamped in by the same reinforcement process that stamps in the ordinary habits via weaker incentives. This hypothesis offers a potential explanation of the compulsiveness not only of drug self-administration, where neuroadaptations have been demonstrated (Robinson et al., 2001), but also of intracranial self-stimulation, where they have not. It is possible that the neuroadaptations of addiction are merely the neuroadaptations of habit formation, stamped in more strongly by drug rewards that can elevate nucleus accumbens dopamine levels 3- to 5-fold more than by conventional rewards that tend to elevate dopamine by a factor of 1.5 or 2 (Hernandez and Hoebel, 1988; Fiorino et al., 1997; Bassareo and Di Chiara, 1999).

Reward Receipt and Reward Prediction

Comparison of the sensed rewards of food, water, and sexual interaction with the unsensed laboratory rewards of brain stimulation and intravenous and intracranial drugs illustrates the difficulty in distinguishing the actual receipt of reward from the receipt of sensory information that reward is coming (prediction of reward). How can one single out a specific event that constitutes the receipt of reward? In the case of a food reward, is the reward received when we see it, touch it, or taste it? This question is not so easily answered as common sense would have us believe.

Rewards are, in the simplest terms, the environmental incentives we tend to approach (Schneirla, 1959). More precisely, they are the environmental incentives we return to after having previously contacted them. It is the return to a reward previously experienced that is the essence of habit and addiction. This is easily understood when the reward is localized in space by one or more of the senses. Consider the case of food reward, however. Once the animal has tasted a sweet substance, it will return to it again and again. However, the return to a previously experienced reward involves the return to reward-associated landmarks as much as it involves return to the reward itself. The animal only finds the reward by approaching the environmental stimuli that point to the location of the reward. As the animal becomes experienced at foraging for food, it identifies and is guided by more and more distal stimuli that, sequentially, help the animal reach the food. Thus, the animal might first learn the smell of a given food and begin to follow the odor trail. Next, the animal might learn the sight of the plants that give off the odor in question and learn to follow the sight path until reaching the odor trail. Finally, the animal might learn the sound of the waterfall that is near the visible landmarks and follow the sound until the landmarks are visible, the sight line until the odor trail is sensed, and then the odor to the ripe and tasty portion of the plant. The sounds, sights, and smells associated with the food are clearly predictors of reward, and the efficiency of the animal increases with the identification of more and more distal predictors of reward, predictors that guide the foraging and that are important for the “error signals” that guide *corrections* to the foraging path.

If the sound, sight, and smell of food are predictors of reward, what is the “receipt” of reward? The widespread assumption is that the taste of a sweet substance (when hungry) or a salty substance (when sodium deficient) constitutes the receipt of reward. In the case of unsensed incentives—brain stimulation reward or intravenous or intracranial drug reward, for example—it is a much more central event that constitutes the receipt of reward. These rewards do not activate any of the five senses (except taste, eventually, when drugs diffuse from the blood to the saliva and reach the taste buds). Yet they have the critical attribute of all rewards; they, by association, establish otherwise neutral stimuli in the environment as things to be approached. The animal trained to lever-press for brain stimulation is guided first by visual stimuli (the sight of the distal lever) and then by tactile stimuli; the stimulation itself has no locus in space. Should we then consider the taste of sweet food simply another sensory predictor of the central process

that really constitutes the rewarding event? In part to separate the subjective and sensory experience of reward from the central events that are critical to habit formation, psychologists have come to use Pavlov's term "reinforcement" in preference to the lay term "reward" (Wise, 1989). Is taste merely a predictor of food reinforcement?

The term "reinforcement" was first coined by Pavlov (in 1903; cited in Pavlov, 1928) to refer to the strengthening of the association between a conditioned stimulus and its unconditioned partner. Pavlov pointed out that the effectiveness of a conditioned stimulus would extinguish if not reinforced by occasional repeat pairings with its associated unconditioned stimulus. By reinforcement he meant something akin to the "stamping in" of stimulus-response associations first discussed by Thorndike (1898). Skinner (1933) and Thorndike (1933) adopted the term reinforcement to the stamping in of response habits (1937); Skinner (1937) posited two forms of reinforcement, one associated with the stamping in of stimulus-stimulus (Pavlovian) associations and one associated with the stamping in of instrumental behavior (which he called "operant" behavior). The brain mechanism of "stamping in" is, of course, the brain mechanism of learning and memory formation, and its locus in the case of habit learning and the question of whether the stamping in of stimulus-stimulus associations involves different structures than the stamping in of response-consequence associations remain matters of speculation (see, for example, White, 1996).

The clearest illustration of the reinforcement process is the stamping in of memory that occurs when a reinforcer such as brain stimulation (Huston and Mueller, 1978) or sucrose (Messier and White, 1984) is given, independent of the animal's performance, following an unrelated learning experience. Post-trial reinforcers (and stressors) improve consolidation of memories for immediately previous events. This post-trial consolidation of learning and memory has been suggested as the essential mechanism of reinforcement, not only the reinforcement of stimulus-stimulus (Pavlovian) associations but also the reinforcement of habit-learning (Lan-dauer, 1969; Pfaff, 1969).

The stamping in of food-rewarded memories appears to depend critically on postingestional consequences of food. If animals are given neutrally flavored foods and each is accompanied by an intragastric glucose load, the animals learn flavor preferences that are proportional to the associated glucose load (Le Magnen, 1959). It takes 3 or 4 days of exposure to learn these preferences, similar to the time it takes for vitamin-deficient rats to learn preferences for flavors associated with the missing vitamin (Harris et al., 1933). Thus, it would appear that the most fundamental event in the identification of sweet taste with food reward is the stamping in of the memory for ingesting sweet substances by some postingestional consequence of those substances. That is to say, the reinforcement process begins some significant time after the taste of the food; the taste of food is, like the smell and sight of food and the sounds that precede the delivery of food, a predictor of reward and not the primary reward itself.

While animals will learn habits that are rewarded by saccharin, a non-nutritive sweet substance (Sheffield

and Roby, 1950), post-trial saccharin is very ineffective, relative to equally preferred concentrations of sucrose, in stamping in post-trial memories (Messier and White, 1984). Moreover, the rewarding effects of saccharin have been demonstrated only in animals that have a history of reinforcement by sweet substances with nutritive value. The first of these in a mammal's life is mother's milk, and rodents begin learning milk-rewarded habits from the first postnatal day (Johanson and Hall, 1979). In all probability, then, the sweet taste of saccharin is a *conditioned* reinforcer, as are most predictors of reward. Consider, for example, the winning of a lottery. The excitement of reward is experienced at the announcement of the winning number and the receipt of the check, not at the postingestional receipt of the food that the money eventually buys.

This is, perhaps, best illustrated with the unsensed rewards of brain stimulation and drugs. Here, the animal has only the reward-associated lever or cue light to approach; the reward itself is not sensed peripherally, either by the distance senses of sight, hearing, and smell or by the proximal senses of taste and touch. Here, the receipt of reward is concurrent with the illumination of the cue light and the click of the relay; these are synonymous with the receipt of reward if not the perceived rewarding events themselves, at least for laboratory rats.

This is an interesting issue because of the work of Schultz and colleagues, showing that the dopamine system—clearly critical for reward function—becomes increasingly responsive to reward predictors and seemingly unresponsive to the reward "itself." Unit recordings in the awake animal present a complex and interesting picture of dopaminergic responsiveness to rewards. When food reward is first earned or discovered, midbrain dopaminergic neurons respond with short-latency phasic bursts of firing (Ljungberg et al., 1992; Schultz et al., 1993; Mirenovicz and Schultz, 1994). In experiments where juice near the animal's mouth was the incentive, the neurons appeared to respond to the taste of the juice (Schultz et al., 1993; Mirenovicz and Schultz, 1994). With repeated testing, however, this phasic response becomes associated with stimuli that predict the presentation of the incentive. In experiments where a small piece of apple was the incentive, the neurons came to respond to the sight of the apple or the click of the latch to the door that hid the apple (Ljungberg et al., 1992). As the neurons began to respond to the distant signals of the rewarding event, they ceased responding to the proximal (taste) cue (Ljungberg et al., 1992; Mirenovicz and Schultz, 1994). In these studies, dopamine neurons were seen as responding to primary rewards "only when the reward occurs unpredictably, either outside of a task or during learning. By contrast, a fully predicted reward does not elicit a response in dopamine neurons, and the response is transferred to the earliest conditioned, reward-predicting stimulus" (Schultz, 1997). This interpretation has been the focus of several recent attempts to understand the role of dopamine in motivated behavior (Schultz et al., 1997; Schultz and Dickinson, 2000; O'Doherty et al., 2002; Schultz, 2002 [this issue of *Neuron*]).

What are the lessons from studies of unsensed incentives for the question of whether dopamine is important for the prediction rather than the receipt of reward? The

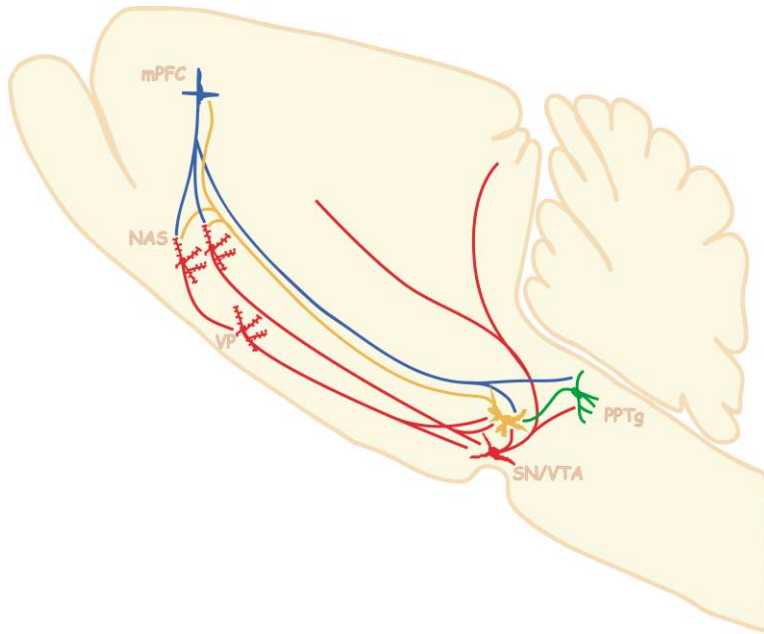


Figure 1. Selected Elements and Connectivity of Brain Reward Circuitry

The mesolimbic dopamine system is in gold. Amphetamine and cocaine are rewarding because they act at the dopamine transporter to elevate nucleus accumbens (NAS) dopamine levels; nicotine is rewarding because of actions on nicotinic cholinergic receptors, expressed at both the cell bodies and the terminals of the mesolimbic system, that result in elevated dopamine release in NAS. Dopamine in NAS inhibits the output neurons of NAS. The normal cholinergic input to these receptors in the VTA is from the pedunculo-pontine tegmental nucleus (PPTg) and the latero-dorsal pontine tegmental nucleus; these nuclei send branching projections to several basal forebrain targets (not shown). Rewarding electrical stimulation of the lateral hypothalamus is thought to be rewarding because it activates fibers to PPTg. The excitatory amino acid (glutamate) projections of medial prefrontal cortex (mPFC) are in blue. Projections from this and other cortical areas that receive mesolimbic dopamine input (amygdala, hippocampus) also project to NAS; amygdala also projects to the substan-

tia nigra and ventral tegmental area (SN/VTA). Phencyclidine is rewarding because it blocks NMDA-type glutamate receptors in NAS and mPFC. Blockade of NMDA receptors in NAS reduces the excitatory input to the GABAergic output neurons. Electrical stimulation of mPFC is rewarding because it causes glutamate release in VTA and dopamine release in NAS. Two subsets of GABAergic projection neurons exit NAS; one projects to the ventral pallidum (VP) and the other to the SN/VTA. GABAergic neurons in VP also project to SN/VTA. Most of the GABAergic projection to SN synapses again on GABAergic neurons; these, in turn, project to the pedunculo-pontine tegmental nucleus, the deep layers of the superior colliculus, and the dorsomedial thalamus. Heroin and morphine have two rewarding actions: inhibition of GABAergic cells that normally hold the mesolimbic dopamine system under inhibitory control (thus morphine disinhibits the dopamine system) and inhibition of output neurons in NAS. Ethanol and cannabis act by unknown mechanisms to increase the firing of the mesolimbic dopamine system and are apparently rewarding for that reason. The habit-forming effects of barbiturates and benzodiazepines appear to be triggered at one or more of the GABAergic links in the circuitry, not necessarily through feedback links to the dopamine system. Caffeine appears to be rewarding through some independent circuitry.

first lesson is that what we tend to designate as the receipt of reward might more accurately be designated as simply a more proximal predictor of reward. Human exultation, if it were objectively studied, would underscore the fact that it is the receipt of reward *predictors* that arouse us most. In the human situation, it is such things as the receipt of money, the receipt of the promise of an assignation, or the receipt of an invitation to compete in the finals of an athletic tournament that elicits the explosive “Yes!” and that marks, as much as anything, the emotional excitement of “receiving” reward. These things are clearly rewards, but they are conditioned rewards, not *primary* rewards; they are rewarding only because of previous learning. These are rewards because of their association with things to come; they are rewards because they predict—just as sweet taste predicts the stamping in of memory by postingestional glucose—something more closely linked to the survival of the individual and the species.

In the case of intravenous or intracranial drug reward, the sensed incentives—sight of the lever or cue light—are learned incentives that arrive tens of seconds or perhaps minutes (Héron et al., 1994; Stathis et al., 1995; Kiyatkin et al., 2000) before a drug such as cocaine can significantly elevate extracellular dopamine. Thus, contact with the approached incentive does not mark the receipt of the *primary* reward. The sight of the lighted cue light signals the receipt of the secondary (learned) incentive just as does the sight of the distant apple. The

click of the lever is no more or less the receipt of cocaine reward than is the click of Ljungberg et al.’s (1992) door the receipt of apple reward. That is to say, in each case the click may be what the subject is “waiting for” but it—like the taste of the apple itself—is only a predictor of the reinforcer, the event that stamps in memory (Landaauer, 1969; Pfaff, 1969; Huston et al., 1974; Messier and White, 1984).

Concluding Remarks

The mesolimbic dopamine system, its cholinergic input from the brainstem, its glutamatergic input from cortical structures including the medial and occipital prefrontal cortex and amygdala, its GABAergic inputs from striatal sources, and, finally, its GABAergic efferents in nucleus accumbens (and *their* glutamatergic inputs from cortical structures) comprise a major portion of the endogenous circuitry through which the pleasures of the flesh come to shape the habits of animal life (Figure 1). The proximity of the mesolimbic system to the nigro-striatal dopamine system—a system widely identified with motor function—has suggested this system to be an interface between motivational and motor mechanisms (Nauta and Domesick, 1978; Mogenson et al., 1980). The rewarding effects of food, water, sexual interaction, lateral hypothalamic brain stimulation, and most drugs of abuse can be eliminated by lesions or blockade of the output neurons of nucleus accumbens or of their dopaminergic input. This system is activated trans-synaptically by the

normal pleasures of life but can be activated directly by the laboratory rewards of intravenous drugs or electrical or chemical brain stimulation.

The activation of this system somehow serves to establish the response habits that are followed reliably by such activation, presumably by augmenting the consolidation—by “stamping in”—the still-active memory traces of the exteroceptive (reward-associated) and interoceptive (response feedback) stimuli that led to the behavior that preceded activation of the system. This stamping in is not done by the sensory events by which we identify rewards so much as by the postsynaptic—and sometimes postingestional—consequences of those sensory events. The sensations of reward are varied; most rewards or incentives can be at least partially identified with both the distal senses of vision, audition, and olfaction and the contact senses of touch and taste. However, laboratory rewards that do not activate any of the five senses can directly activate the system even more strongly than can the natural pleasures of life. Thus, the five senses themselves are responsible not for the receipt of reward but rather the prediction of the stamping-in process. Indeed, the mesolimbic dopamine system is excited as much or more by the distant sensory message that guarantees a reward or incentive is coming as by the contact sense message that a reward has arrived. This raises the possibility that the neural circuitry of learned habits is not only stamped in after rewards are received but is also primed by the stimuli that predict that rewards are coming.

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References

Ahmed, S.H., and Koob, G.F. (1998). Transition from moderate to excessive drug intake: Change in hedonic set point. *Science* 282, 298–300.

Aizman, O., Brismar, H., Uhlen, P., Zettergren, E., Levey, A.I., Forssberg, H., Greengard, P., and Aperia, A. (2000). Anatomical and physiological evidence for D1 and D2 dopamine receptor colocalization in neostriatal neurons. *Nat. Neurosci.* 3, 226–230.

Annau, Z., Heffner, R., and Koob, G.F. (1974). Electrical self-stimulation of single and multiple loci: Long term observations. *Physiol. Behav.* 13, 281–290.

Bartoletti, M., Gaiardi, M., Gubellini, G., Bacchi, A., and Babbini, M. (1983). Long-term sensitization to the excitatory effects of morphine. A motility study in post-dependent rats. *Neuropharmacology* 22, 1193–1196.

Bassareo, V., and Di Chiara, G. (1999). Modulation of feeding-induced activation of mesolimbic dopamine transmission by appetitive stimuli and its relation to motivational state. *Eur. J. Neurosci.* 11, 4389–4397.

Berke, J.D., and Hyman, S.E. (2000). Addiction, dopamine, and the molecular mechanisms of memory. *Neuron* 25, 515–532.

Bielajew, C., and Shizgal, P. (1982). Behaviorally derived measures of conduction velocity in the substrate for rewarding medial forebrain bundle stimulation. *Brain Res.* 237, 107–119.

Bielajew, C., and Shizgal, P. (1986). Evidence implicating descending fibers in self-stimulation of the medial forebrain bundle. *J. Neurosci.* 6, 919–929.

Bielajew, C., LaPointe, M., Kiss, I., and Shizgal, P. (1982). Absolute and relative refractory periods of the substrates for lateral hypothal-

amic and ventral midbrain self-stimulation. *Physiol. Behav.* 28, 125–132.

Black, J., Belluzzi, J., and Stein, L. (1985). Reinforcement delay of one second severely impairs acquisition of brain self-stimulation. *Brain Res.* 359, 113–119.

Bouyer, J.J., Park, D.H., Joh, T.H., and Pickel, V.M. (1984). Chemical and structural analysis of the relation between cortical inputs and tyrosine hydroxylase-containing terminals in rat neostriatum. *Brain Res.* 302, 267–275.

Bozarth, M.A., and Wise, R.A. (1981). Intracranial self-administration of morphine into the ventral tegmental area in rats. *Life Sci.* 28, 551–555.

Bozarth, M.A., and Wise, R.A. (1984). Anatomically distinct opiate receptor fields mediate reward and physical dependence. *Science* 224, 516–517.

Bozarth, M.A., and Wise, R.A. (1985). Toxicity associated with long-term intravenous heroin and cocaine self-administration in the rat. *JAMA* 254, 81–83.

Cameron, D.L., and Williams, J.T. (1993). Dopamine D1 receptors facilitate transmitter release. *Nature* 366, 344–347.

Carlezon, W.A., Jr., and Wise, R.A. (1996a). Rewarding actions of phencyclidine and related drugs in nucleus accumbens shell and frontal cortex. *J. Neurosci.* 16, 3112–3122.

Carlezon, W.A., Jr., and Wise, R.A. (1996b). Microinjections of phencyclidine (PCP) and related drugs into nucleus accumbens shell potentiate lateral hypothalamic brain stimulation reward. *Psychopharmacology (Berl.)* 128, 413–420.

Carlezon, W.A., Jr., Devine, D.P., and Wise, R.A. (1995). Habit-forming actions of nomifensine in nucleus accumbens. *Psychopharmacology (Berl.)* 122, 194–197.

Carr, G.D., and White, N.M. (1983). Conditioned place preference from intra-accumbens but not intra-caudate amphetamine injections. *Life Sci.* 33, 2551–2557.

Cicero, T.J. (1980). Animal models of alcoholism. In *Animal Models in Alcohol Research*, K. Eriksson, J.D. Sinclair, and K. Kiianmaa, eds. (New York: Academic), pp. 99–118.

Clarke, P.B.S., and Pert, A. (1985). Autoradiographic evidence for nicotine receptors on nigrostriatal and mesolimbic dopaminergic neurons. *Brain Res.* 348, 355–358.

Clark, D., and White, F.J. (1987). Review: D1 dopamine receptor—the search for a function: A critical evaluation of the D1/D2 dopamine receptor classification and its function implications. *Synapse* 7, 347–388.

Colle, L.M., and Wise, R.A. (1988). Effects of nucleus accumbens amphetamine on lateral hypothalamic brain stimulation reward. *Brain Res.* 459, 361–368.

Coons, E.E., Levak, M., and Miller, N.E. (1965). Lateral hypothalamus: Learning of food-seeking response motivated by electrical stimulation. *Science* 150, 1320–1321.

Corbett, D., Silva, L.R., and Stellar, J.R. (1985). An investigation of the factors affecting development of frontal cortex self-stimulation. *Physiol. Behav.* 34, 89–95.

David, V., and Cazala, P. (2000). Anatomical and pharmacological specificity of the rewarding effect elicited by microinjections of morphine into the nucleus accumbens of mice. *Psychopharmacology (Berl.)* 150, 24–34.

David, V., Durkin, T.P., and Cazala, P. (1997). Self-administration of the GABAA antagonist bicuculline into the ventral tegmental area in mice: dependence on D2 dopaminergic mechanisms. *Psychopharmacology (Berl.)* 130, 85–90.

David, V., Durkin, T.P., and Cazala, P. (2002). Differential effects of the dopamine D(2)/D(3) receptor antagonist sulpiride on self-administration of morphine into the ventral tegmental area or the nucleus accumbens. *Psychopharmacology (Berl.)* 160, 307–317.

Deneau, G., Yanagita, T., and Seevers, M.H. (1969). Self-administration of psychoactive substances by the monkey: A measure of psychological dependence. *Psychopharmacologia* 16, 30–48.

Devine, D.P., and Wise, R.A. (1994). Self-administration of morphine,

- DAMGO, and DPDPE into the ventral tegmental area of rats. *J. Neurosci.* 14, 1978–1984.
- Devine, D.P., Leone, P., Pocock, D., and Wise, R.A. (1993). Differential involvement of ventral tegmental mu, delta and kappa opioid receptors in modulation of basal mesolimbic dopamine release: in vivo microdialysis studies. *J. Pharmacol. Exp. Ther.* 266, 1236–1246.
- Downs, A.W., and Eddy, N.B. (1932). The effect of repeated doses of cocaine on the dog. *J. Pharmacol. Exp. Ther.* 46, 195–198.
- Falk, J.L., Samson, H.M., and Winger, G. (1972). Behavioural maintenance of high concentrations of blood ethanol and physical dependence in the rat. *Science* 177, 811–813.
- Fiorino, D.F., and Phillips, A.G. (1999). Facilitation of sexual behavior in male rats following d-amphetamine-induced behavioral sensitization. *Psychopharmacology (Berl.)* 142, 200–208.
- Fiorino, D.F., Coury, A., and Phillips, A.G. (1997). Dynamic changes in nucleus accumbens dopamine efflux during the Coolidge effect in male rats. *J. Neurosci.* 17, 4849–4855.
- Forster, G.L., Yeomans, J.S., Takeuchi, J., and Blaha, C.D. (2002). M5 muscarinic receptors are required for prolonged accumbal dopamine release after electrical stimulation of the pons in mice. *J. Neurosci.* 22, RC190.
- Fouriez, G., and Randall, D. (1997). The cost of delaying rewarding brain stimulation. *Behav. Brain Res.* 87, 111–113.
- Fouriez, G., and Wise, R.A. (1984). Current-distance relation for rewarding brain stimulation. *Behav. Brain Res.* 14, 85–89.
- Frank, R.A., Martz, S., and Pommering, T. (1988). The effect of chronic cocaine on self-stimulation train-duration thresholds. *Pharmacol. Biochem. Behav.* 29, 755–758.
- Gerber, G.J., and Wise, R.A. (1989). Pharmacological regulation of intravenous cocaine and heroin self-administration in rats: a variable dose paradigm. *Pharmacol. Biochem. Behav.* 32, 527–531.
- Gerfen, C.R. (1992). The neostriatal mosaic: multiple levels of compartmental organization. *Trends Neurosci.* 15, 133–139.
- Gerhardt, G.A., Pang, K., and Rose, G.M. (1987). In vivo electrochemical demonstration of the presynaptic actions of phencyclidine in rat caudate nucleus. *J. Pharmacol. Exp. Ther.* 241, 714–721.
- German, D.C., and Bowden, D.M. (1974). Catecholamine systems as the neural substrate for intracranial self-stimulation: A hypothesis. *Brain Res.* 73, 381–419.
- Glickman, S.E., and Schiff, B.B. (1967). A biological theory of reinforcement. *Psychol. Rev.* 74, 81–109.
- Goeders, N.E., Lane, J.D., and Smith, J.E. (1984). Self-administration of methionine enkephalin into the nucleus accumbens. *Pharmacol. Biochem. Behav.* 20, 451–455.
- Gratton, A., and Wise, R.A. (1985). Hypothalamic reward mechanism: two first-stage fiber populations with a cholinergic component. *Science* 227, 545–548.
- Grimm, J.W., Hope, B.T., Wise, R.A., and Shaham, Y. (2001). Incubation of cocaine craving during withdrawal. *Nature* 412, 141–142.
- Harmer, C.J., and Phillips, G.D. (1998). Enhanced appetitive conditioning following repeated pretreatment with d-amphetamine. *Behav. Pharmacol.* 9, 299–308.
- Harris, L.J., Clay, J., Hargreaves, F.J., and Ward, A. (1933). Appetite and choice of diet: the ability of the vitamin B deficient rat to discriminate between diets containing and lacking the vitamin. *Proc. R. Soc. Lond. B Biol. Sci.* 113, 161–190.
- Heidbreder, C.A., Thompson, A.C., and Shippenberg, T.S. (1996). Role of extracellular dopamine in the initiation and long-term expression of behavioral sensitization to cocaine. *J. Pharmacol. Exp. Ther.* 278, 490–502.
- Hernandez, L., and Hoebel, B.G. (1988). Food reward and cocaine increase extracellular dopamine in the nucleus accumbens as measured by microdialysis. *Life Sci.* 42, 1705–1712.
- Héron, C., Costentin, J., and Bonnet, J.J. (1994). Evidence that pure uptake inhibitors including cocaine interact slowly with the dopamine neuronal carrier. *Eur. J. Pharmacol.* 264, 391–398.
- Hoebel, B.G., Monaco, A.P., Hernandez, L., Aulisi, E.F., Stanley, B.G., and Lenard, L. (1983). Self-injection of amphetamine directly into the brain. *Psychopharmacology (Berl.)* 81, 158–163.
- Horger, B.A., Shelton, K., and Schenk, S. (1990). Preexposure sensitizes rats to the rewarding effects of cocaine. *Pharmacol. Biochem. Behav.* 37, 707–711.
- Huston, J.P., and Mueller, C.C. (1978). Enhanced passive avoidance learning and appetitive T-maze learning with post-trial rewarding hypothalamic stimulation. *Brain Res. Bull.* 3, 265–270.
- Huston, J.P., Mondadori, C., and Waser, P.G. (1974). Facilitation of learning by reward of post-trial memory processes. *Experientia* 30, 1038–1040.
- Hyman, S.E., and Malenka, R.C. (2001). Addiction and the brain: the neurobiology of compulsion and its persistence. *Nat. Rev. Neurosci.* 2, 695–703.
- Ikemoto, S., and Wise, R.A. (2002). Rewarding effects of carbachol and neostigmine in the posterior ventral tegmental area. *J. Neurosci.*, in press.
- Ikemoto, S., Glazier, B.S., Murphy, J.M., and McBride, W.J. (1997a). Role of dopamine D₁ and D₂ receptors in the nucleus accumbens in mediating reward. *J. Neurosci.* 17, 8580–8587.
- Ikemoto, S., Kohl, R.R., and McBride, W.J. (1997b). GABA(A) receptor blockade in the anterior ventral tegmental area increases extracellular levels of dopamine in the nucleus accumbens of rats. *J. Neurochem.* 69, 137–143.
- Ikemoto, S., Murphy, J.M., and McBride, W.J. (1997c). Self-infusion of GABA_A antagonists directly into the ventral tegmental area and adjacent regions. *Behav. Neurosci.* 111, 369–380.
- Ikemoto, S., Glazier, B.S., Murphy, J.M., and McBride, W.J. (1998a). Rats self-administer carbachol directly into the nucleus accumbens. *Physiol. Behav.* 63, 811–814.
- Ikemoto, S., Murphy, J.M., and McBride, W.J. (1998b). Regional differences within the rat ventral tegmental area for muscimol self-infusions. *Pharmacol. Biochem. Behav.* 61, 87–92.
- Jaffe, J.H. (1985). Drug addiction and drug abuse. In *The Pharmacological Basis of Therapeutics*, A.G. Gilman and L.S. Goodman, eds. (New York: Macmillan), pp. 532–581.
- Johanson, I.B., and Hall, W.G. (1979). Appetitive learning in 1-day-old rat pups. *Science* 205, 419–421.
- Johanson, C.E., Balster, R.L., and Bonese, K. (1976). Self-administration of psychomotor stimulant drugs: The effects of unlimited access. *Pharmacol. Biochem. Behav.* 4, 45–51.
- Johnson, A.K., and Epstein, A.N. (1975). The cerebral ventricles as the avenue for the dipsogenic action of intracranial angiotensin. *Brain Res.* 86, 399–418.
- Johnson, S.W., and North, R.A. (1992). Opioids excite dopamine neurons by hyperpolarization of local interneurons. *J. Neurosci.* 12, 483–488.
- Kalivas, P.W., and Duffy, P. (1987). Sensitization to repeated morphine injection in the rat: possible involvement of A10 dopamine neurons. *J. Pharmacol. Exp. Ther.* 241, 204–212.
- Kalivas, P.W., and Duffy, P. (1995). D1 receptors modulate glutamate transmission in the ventral tegmental area. *J. Neurosci.* 15, 5379–5388.
- Kalivas, P.W., Widerlov, E., Stanley, D., Breese, G., and Prange, A.J. (1983). Enkephalin action on the mesolimbic system: A dopamine-dependent and a dopamine-independent increase in locomotor activity. *J. Pharmacol. Exp. Ther.* 227, 229–237.
- Kiyatkin, E.A., Kiyatkin, D.E., and Rebec, G.V. (2000). Phasic inhibition of dopamine uptake in nucleus accumbens induced by intravenous cocaine in freely behaving rats. *Neuroscience* 98, 729–741.
- Koob, G.F. (1996). Drug addiction: the yin and yang of hedonic homeostasis. *Neuron* 16, 893–896.
- Koob, G.F., and Bloom, F.E. (1988). Cellular and molecular mechanisms of drug dependence. *Science* 242, 715–723.
- Koob, G.F., and Le Moal, M. (2001). Drug addiction, dysregulation of reward, and allostasis. *Neuropsychopharmacology* 24, 97–129.
- Kofman, O., McGlynn, S.M., Olmstead, M.C., and Yeomans, J.S. (1990). Differential effects of atropine, procaine and dopamine in

- the rat ventral tegmentum on lateral hypothalamic rewarding brain stimulation. *Behav. Brain Res.* 38, 55–68.
- Kokkinidis, L., and McCarter, B.D. (1990). Postcocaine depression and sensitization of brain-stimulation reward: Analysis of reinforcement and performance effects. *Pharmacol. Biochem. Behav.* 36, 463–471.
- Kokkinidis, L., Zacharko, R.M., and Preedy, P.A. (1980). Post-amphetamine depression of self-stimulation responding from the substantia nigra: Reversal by tricyclic antidepressants. *Pharmacol. Biochem. Behav.* 13, 379–383.
- Laakso, A., Mohn, A.R., Gainetdinov, R.R., and Caron, M.G. (2002). Experimental genetic approaches to addiction. *Neuron* 36, this issue, 213–228.
- Landauer, T.K. (1969). Reinforcement as consolidation. *Psychol. Rev.* 76, 82–96.
- Leith, N.J., and Barrett, R.J. (1976). Amphetamine and the reward system: Evidence for tolerance and post-drug depression. *Psychopharmacologia* 46, 19–25.
- Le Magnen, J. (1959). Effects des administrations post-prandiales de glucose sur l'établissement des appétits. *Comptes Rendus des Seances de la Societe de Biologie (Paris)* 153, 212–215.
- Lepore, M., and Franklin, K.B.J. (1992). Modelling drug kinetics with brain stimulation: Dopamine antagonists increase self-stimulation. *Pharmacol. Biochem. Behav.* 41, 489–496.
- Leshner, A.I. (1999). Science-based views of drug addiction and its treatment. *JAMA* 282, 1314–1316.
- Lester, D. (1966). Self-selection of alcohol by animals, human variation and the etiology of alcoholism: A critical review. *Q. J. Stud. Alcohol* 27, 395–438.
- Lett, B.T. (1989). Repeated exposures intensify rather than diminish the rewarding effects of amphetamine, morphine, and cocaine. *Psychopharmacology (Berl.)* 98, 357–362.
- Ljungberg, T., Apicella, P., and Schultz, W. (1992). Responses of monkey dopamine neurons during learning of behavioral reactions. *J. Neurophysiol.* 67, 145–163.
- MacDonnell, M.F., and Flynn, J.P. (1966a). Sensory control of hypothalamic attack. *Anim. Behav.* 14, 399–405.
- MacDonnell, M.F., and Flynn, J.P. (1966b). Control of sensory fields by stimulation of hypothalamus. *Science* 152, 1046–1048.
- McLellan, A.T., Lewis, D.C., O'Brien, C.P., and Kleber, H.D. (2000). Drug dependence, a chronic medical illness: implications for treatment, insurance, and outcomes evaluation. *JAMA* 284, 1689–1695.
- Mello, N.K. (1973). A review of methods to induce alcohol addiction in animals. *Pharmacol. Biochem. Behav.* 1, 89–101.
- Mendelson, J., and Chorover, S.L. (1965). Lateral hypothalamic stimulation in satiated rats: T-maze learning for food. *Science* 149, 559–561.
- Messier, C., and White, N.M. (1984). Contingent and non-contingent actions of sucrose and saccharin reinforcers: Effects on taste preference and memory. *Physiol. Behav.* 32, 195–203.
- Mirenowicz, J., and Schultz, W. (1994). Importance of unpredictedness for reward responses in primate dopamine neurons. *J. Neurophysiol.* 72, 1024–1027.
- Mitchell, J.B., and Stewart, J. (1990). Facilitation of sexual behaviors in the male rat in the presence of stimuli previously paired with systemic injections of morphine. *Pharmacol. Biochem. Behav.* 35, 367–372.
- Mogenson, G.J., Jones, D.L., and Yim, C.Y. (1980). From motivation to action: Functional interface between the limbic system and the motor system. *Prog. Neurobiol.* 14, 69–97.
- Murray, B., and Shizgal, P. (1994). Evidence implicating both slow- and fast-conducting fibers in the rewarding effect of medial forebrain bundle stimulation. *Behav. Brain Res.* 63, 47–60.
- Museo, E., and Wise, R.A. (1994). Place preference conditioning with ventral tegmental injections of cytosine. *Life Sci.* 55, 1179–1186.
- Nauta, W.J.H., and Domesick, V.B. (1978). Crossroads of limbic and striatal circuitry: hypothalamo-nigral connections. In *Limbic Mechanisms*, K.E. Livingston and O. Hornykiewicz, eds. (New York: Plenum Press), pp. 75–93.
- Nestler, E.J. (1992). Molecular mechanisms of drug addiction. *J. Neurosci.* 12, 2439–2450.
- Nestler, E.J. (2001). Molecular basis of long-term plasticity underlying addiction. *Nat. Rev. Neurosci.* 2, 119–128.
- O'Brien, C.P., Childress, A.R., Ehrman, R., and Robbins, S.W. (1998). Conditioning factors in drug abuse: can they explain compulsion? *J. Psychopharmacol.* 12, 15–22.
- O'Doherty, J.P., Deichmann, R., Critchley, H.D., and Dolan, R.J. (2002). Neural responses during anticipation of a primary taste reward. *Neuron* 33, 815–826.
- Olds, J. (1958a). Self-stimulation of the brain. *Science* 127, 315–324.
- Olds, J. (1958b). Satiation effects in self-stimulation of the brain. *J. Comp. Physiol. Psychol.* 51, 675–678.
- Olds, J. (1959). Self-stimulation experiments and differentiated reward systems. In *Reticular Formation of the Brain*, H. Jasper, L.D. Proctor, R.S. Knighton, W.C. Noshay, and R.T. Costello, eds. (Boston: Little, Brown and Company), pp. 671–687.
- Olds, M.E. (1982). Reinforcing effects of morphine in the nucleus accumbens. *Brain Res.* 237, 429–440.
- Olds, J., and Milner, P.M. (1954). Positive reinforcement produced by electrical stimulation of septal area and other regions of rat brain. *J. Comp. Physiol. Psychol.* 47, 419–427.
- Olds, M.E., and Olds, J. (1963). Approach-avoidance analysis of rat dienecephalon. *J. Comp. Neurol.* 120, 259–295.
- Olds, J., and Olds, M.E. (1965). Drives, rewards, and the brain. In *New Directions in Psychology*, T.M. Newcombe, ed. (New York: Holt, Rinehart and Winston), pp. 327–410.
- Olds, J., Yuwiler, A., Olds, M.E., and Yun, C. (1964). Neurohumors in hypothalamic substrates of reward. *Am. J. Physiol.* 207, 242–254.
- Paulson, P.E., and Robinson, T.E. (1995). Amphetamine-induced time-dependent sensitization of dopamine neurotransmission in the dorsal and ventral striatum: a microdialysis study in behaving rats. *Synapse* 19, 56–65.
- Pavlov, I.P. (1928). *Lectures on conditioned reflexes* (New York: International Publishers).
- Pfaff, D. (1969). Parsimonious biological models of memory and reinforcement. *Psychol. Rev.* 76, 70–81.
- Phelps, P.E., Houser, C.R., and Vaughn, J.E. (1985). Immunocytochemical localization of choline acetyltransferase within the rat neostriatum: A correlated light and electron microscopic study of cholinergic neurons and synapses. *J. Comp. Neurol.* 238, 286–307.
- Phillips, A.G., and LePiane, F.G. (1980). Reinforcing effects of morphine microinjection into the ventral tegmental area. *Pharmacol. Biochem. Behav.* 12, 965–968.
- Piazza, P.V., Deminiere, J.M., Le Moal, M., and Simon, H. (1990). Stress- and pharmacologically-induced behavioral sensitization increases vulnerability to acquisition of amphetamine self-administration. *Brain Res.* 514, 22–26.
- Pickens, R., and Thompson, T. (1968). Cocaine-reinforced behavior in rats: Effects of reinforcement magnitude and fixed-ratio size. *J. Pharmacol. Exp. Ther.* 161, 122–129.
- Rada, P.V., Mark, G.P., Yeomans, J.J., and Hoebel, B.G. (2000). Acetylcholine release in ventral tegmental area by hypothalamic self-stimulation, eating, and drinking. *Pharmacol. Biochem. Behav.* 65, 375–379.
- Ranaldi, R., and Wise, R.A. (2001). Blockade of D1 dopamine receptors in the ventral tegmental area decreases cocaine reward: Possible role for dendritically released dopamine. *J. Neurosci.* 21, 5841–5846.
- Ranaldi, R., Pocock, D., Zereik, R., and Wise, R.A. (1999). Dopamine fluctuations in the nucleus accumbens during maintenance, extinction, and reinstatement of intravenous D-amphetamine self-administration. *J. Neurosci.* 19, 4102–4109.
- Redgrave, P., and Horrell, R.I. (1976). Potentiation of central reward by localized perfusion of acetylcholine and 6-hydroxytryptamine. *Nature* 262, 305–307.

- Rick, C.E., and Lacey, M.G. (1994). Rat substantia nigra pars reticulata neurons are tonically inhibited via GABA_A, but not GABA_B, receptors in vitro. *Brain Res.* 659, 133–137.
- Roberts, A.J., Heyser, C.J., Cole, M., Griffin, P., and Koob, G.F. (2000). Excessive ethanol drinking following a history of dependence: animal model of allostasis.
- Robinson, T.E., and Berridge, K.C. (1993). The neural basis of drug craving: An incentive-sensitization theory of addiction. *Brain Res. Brain Res. Rev.* 18, 247–292.
- Robinson, T.E., and Berridge, K.C. (2000). The psychology and neurobiology of addiction: an incentive-sensitization view. *Addiction Suppl.* 2, S91–S117.
- Robinson, J.H., and Pritchard, W.S. (1995). Differentiating habits and addictions: the evidence that nicotine is not 'addictive'. In *Effects of Nicotine on Biological Systems II*, P.B.S. Clarke, M. Quik, F. Adlkofer, and K. Thurau, eds. (Basel: Birkhäuser Verlag), pp. 273–278.
- Robinson, T.E., Gorny, G., Mitton, E., and Kolb, B. (2001). Cocaine self-administration alters the morphology of dendrites and dendritic spines in the nucleus accumbens and neocortex. *Synapse* 39, 257–266.
- Routtenberg, A. (1972). Intracranial chemical injection and behavior: A critical review. *Behav. Biol.* 7, 601–641.
- Routtenberg, A. (1976). Self-stimulation pathways: origins and terminations—a three-stage technique. In *Brain-Stimulation Reward*, A. Wauquier and E.T. Rolls, eds. (New York: Elsevier), pp. 31–39.
- Routtenberg, A., and Lindy, J. (1965). Effects of the availability of rewarding septal and hypothalamic stimulation on bar pressing for food under conditions of deprivation. *J. Comp. Physiol. Psychol.* 60, 158–161.
- Routtenberg, A., and Simpson, J.B. (1974). Carbachol-induced drinking at ventricular and subfornical organ sites. *Life Sci.* 10, 481–490.
- Routtenberg, A., and Sloan, M. (1972). Self-stimulation in the frontal cortex of *Rattus norvegicus*. *Behav. Biol.* 7, 567–572.
- Schneirla, T.C. (1959). An evolutionary and developmental theory of biphasic processes underlying approach and withdrawal. In *Nebraska Symposium on Motivation*, M.R. Jones, ed. (Lincoln: University of Nebraska Press), pp. 1–42.
- Schulkin, J., McEwen, B.S., and Gold, P.W. (1994). Allostasis, amygdala, and anticipatory angst. *Neurosci. Biobehav. Rev.* 18, 385–396.
- Schulteis, G., Markou, A., Cole, M., and Koob, G.F. (1995). Decreased brain reward produced by ethanol withdrawal. *Proc. Natl. Acad. Sci. USA* 92, 5880–5884.
- Schultz, W. (1997). Dopamine neurons and their role in reward mechanisms. *Curr. Opin. Neurobiol.* 7, 191–197.
- Schultz, W. (2002). Getting formal with dopamine and reward. *Neuron* 36, this issue, 241–263.
- Schultz, W., and Dickinson, A. (2000). Neuronal coding of prediction errors. *Annu. Rev. Neurosci.* 23, 473–500.
- Schultz, W., Apicella, P., and Ljungberg, T. (1993). Responses of monkey dopamine neurons to reward and conditioned stimuli during successive steps of learning a delayed response task. *J. Neurosci.* 13, 900–913.
- Schultz, W., Dayan, P., and Montague, P.R. (1997). A neural substrate of prediction and reward. *Science* 275, 1593–1599.
- Segal, D.S., and Mandell, A.J. (1974). Long-term administration of d-amphetamine: Progressive augmentation of motor activity and stereotypy. *Pharmacol. Biochem. Behav.* 2, 249–255.
- Shalev, U., Morales, M., Hope, B., Yap, J., and Shaham, Y. (2001). Time-dependent changes in extinction behavior and stress-induced reinstatement of drug seeking following withdrawal from heroin in rats. *Psychopharmacology (Berl.)* 156, 98–107.
- Sheffield, F.D., and Roby, T.B. (1950). Reward value of a non-nutritive sweet taste. *J. Comp. Physiol. Psychol.* 43, 471–481.
- Shippenberg, T.S., and Heidbreder, C. (1995). Sensitization to the conditioned rewarding effects of cocaine: pharmacological and temporal characteristics. *J. Pharmacol. Exp. Ther.* 273, 808–815.
- Skinner, B.F. (1933). The rate of establishment of a discrimination. *J. Gen. Psychol.* 9, 302–350.
- Skinner, B.F. (1937). Two types of conditioned reflex: A reply to Konorski and Miller. *J. Gen. Psychol.* 16, 272–279.
- Starr, M. (1987). Opposing roles of dopamine D1 and D2 receptors in nigral gamma-[3H]aminobutyric acid release? *J. Neurochem.* 49, 1042–1049.
- Stathis, M., Scheffel, U., Lever, S.Z., Boja, J.W., Carroll, F.I., and Kuhar, M.J. (1995). Rate of binding of various inhibitors at the dopamine transporter in vivo. *Psychopharmacology (Berl.)* 119, 376–384.
- Sterling, P., and Eyer, J. (1988). Allostasis: A new paradigm to explain arousal pathology. In *Handbook of Life Stress, Cognition and Health*, S. Fisher and J. Reason, eds. (New York: Wiley), pp. 629–649.
- Stinus, L., Winnock, M., and Kelley, A.E. (1985). Chronic neuroleptic treatment and mesolimbic dopamine denervation induce behavioural supersensitivity to opiates. *Psychopharmacology (Berl.)* 85, 323–328.
- Stinus, L., Nadaud, D., Jauregui, J., and Kelley, A.E. (1986). Chronic treatment with five different neuroleptics elicits behavioral supersensitivity to opiate infusion into the nucleus accumbens. *Biol. Psychiatry* 21, 34–48.
- Stolerman, I.P., and Jarvis, M.J. (1995). The scientific case that nicotine is addictive. *Psychopharmacology (Berl.)* 117, 2–10.
- Sugita, S., Johnson, S.W., and North, R.A. (1992). Synaptic inputs to GABA_A and GABA_B receptors originate from discrete afferent neurons. *Neurosci. Lett.* 134, 207–211.
- Surmeier, D.J., Song, W.J., and Yan, Z. (1996). Coordinated expression of dopamine receptors in neostriatal medium spiny neurons. *J. Neurosci.* 16, 6579–6591.
- Taylor, J.R., and Horger, B.A. (1999). Enhanced responding for conditioned reward produced by intra-accumbens amphetamine is potentiated after cocaine sensitization. *Psychopharmacology (Berl.)* 142, 31–40.
- Thompson, T., and Schuster, C.R. (1964). Morphine self-administration, food-reinforced, and avoidance behaviors in rhesus monkeys. *Psychopharmacologia* 5, 87–94.
- Thorndike, E.L. (1898). Animal intelligence: An experimental study of the associative processes in animals. *Psychol. Monogr.* 8, 1–109.
- Thorndike, E.L. (1933). A theory of the action of the after-effects of a connection upon it. *Psychol. Rev.* 40, 434–439.
- Tornatzky, W., and Miczek, K. (2000). Cocaine self-administration "binges": transition from behavioral and autonomic regulation toward homeostatic dysregulation in rats. *Psychopharmacology (Berl.)* 148, 289–298.
- Vezina, P., Pierre, P.J., and Lorrain, D.S. (1999). The effect of previous exposure to amphetamine on drug-induced locomotion and self-administration of a low dose of the drug. *Psychopharmacology (Berl.)* 147, 125–134.
- Walaas, I., and Fonnum, F. (1979). The distribution and origin of glutamate decarboxylase and choline acetyltransferase in ventral pallidum and other basal forebrain regions. *Brain Res.* 177, 325–336.
- Walters, J.R., Bergstrom, E.A., Carlson, J.H., Chase, T.N., and Brain, A.R. (1987). D₂ dopamine receptor activation required for post-synaptic expression of D₂ agonist effects. *Science* 236, 719–722.
- Watkins, S.S., Stinus, L., Koob, G.F., and Markou, A. (2000). Reward and somatic changes during precipitated nicotine withdrawal in rats: centrally and peripherally mediated effects. *J. Pharmacol. Exp. Ther.* 292, 1053–1064.
- Weeks, J.R. (1962). Experimental morphine addiction: Method for automatic intravenous injections in unrestrained rats. *Science* 143, 143–144.
- Weiner, D.M., Levey, A.I., and Brann, M.R. (1990). Expression of muscarinic acetylcholine and dopamine receptor mRNAs in rat basal ganglia. *Proc. Natl. Acad. Sci. USA* 87, 7050–7054.
- Welzl, H., Kuhn, G., and Huston, J.P. (1989). Self-administration of small amounts of morphine through glass micropipettes into the ventral tegmental area of the rat. *Neuropharmacology* 28, 1017–1023.

- West, R. (1992). Nicotine addiction: a re-analysis of the arguments. *Psychopharmacology (Berl.)* 108, 408–410.
- White, N.M. (1996). Addictive drugs as reinforcers: multiple partial actions on memory systems. *Addiction* 91, 921–949.
- White, F.J., and Kalivas, P.W. (1998). Neuroadaptations involved in amphetamine and cocaine addiction. *Drug Alcohol Depend.* 51, 141–153.
- Wise, R.A. (1974). Lateral hypothalamic electrical stimulation: does it make animals 'hungry'? *Brain Res.* 67, 187–209.
- Wise, R.A. (1987). Intravenous drug self-administration: A special case of positive reinforcement. In *Methods of Assessing the Reinforcing Properties of Abused Drugs*, M.A. Bozarth, ed. (New York: Springer-Verlag), pp. 117–141.
- Wise, R.A. (1988). The neurobiology of craving: Implications for understanding and treatment of addiction. *J. Abnorm. Psychol.* 97, 118–132.
- Wise, R.A. (1989). The brain and reward. In *The Neuropharmacological Basis of Reward*, J.M. Liebman and S.J. Cooper, eds. (Oxford: Oxford University Press), pp. 377–424.
- Wise, R.A., and Hoffman, D.C. (1992). Localization of drug reward mechanisms by intracranial injections. *Synapse* 10, 247–263.
- Wise, R.A., Leone, P., Rivest, R., and Leeb, K. (1995a). Elevations of nucleus accumbens dopamine and DOPAC levels during intravenous heroin self-administration. *Synapse* 21, 140–148.
- Wise, R.A., Newton, P., Leeb, K., Burnette, B., Pocock, P., and Justice, J.B. (1995b). Fluctuations in nucleus accumbens dopamine concentration during intravenous cocaine self-administration in rats. *Psychopharmacology (Berl.)* 120, 10–20.
- Wolf, M.E., White, F.J., Nassar, R., Broderson, R.J., and Khansa, M.R. (1993). Differential development of autoreceptor subsensitivity and enhanced dopamine release during amphetamine sensitization. *J. Pharmacol. Exp. Ther.* 264, 249–255.
- Woods, J.H. (1990). Abuse liability and the regulatory control of therapeutic drugs: untested assumptions. *Drug Alcohol Depend.* 25, 229–233.
- Woods, J.H., and Schuster, C.R. (1971). Opiates as reinforcing stimuli. In *Stimulus Properties of Drugs*, T. Thompson and R. Pickens, eds. (New York: Appleton, Century, Crofts), pp. 163–175.
- Woolverton, W.L. (1986). Effects of a D₁ and a D₂ dopamine antagonist on the self-administration of cocaine and pibredil by rhesus monkeys. *Pharmacol. Biochem. Behav.* 24, 531–535.
- Yeomans, J.S. (1979). Absolute refractory periods of self-stimulation neurons. *Physiol. Behav.* 22, 911–919.
- Yeomans, J.S. (1989). Two substrates for medial forebrain bundle self-stimulation: Myelinated axons and dopamine axons. *Neurosci. Biobehav. Rev.* 13, 91–98.
- Yeomans, J.S., and Baptista, M. (1997). Both nicotinic and muscarinic receptors in ventral tegmental area contribute to brain-stimulation reward. *Pharmacol. Biochem. Behav.* 57, 915–921.
- Yeomans, J.S., Kofman, O., and McFarlane, V. (1985). Cholinergic involvement in lateral hypothalamic rewarding brain stimulation. *Brain Res.* 329, 19–26.
- Yeomans, J.S., Mathur, A., and Tampakeras, M. (1993). Rewarding brain stimulation: Role of tegmental cholinergic neurons that activate dopamine neurons. *Behav. Neurosci.* 107, 1077–1087.
- Yeomans, J.S., Takeuchi, J., Baptista, M., Flynn, D.D., Lepik, K., Norega, J., Fulton, J., and Ralph, M.R. (2000). Brain-stimulation reward thresholds raised by an antisense oligonucleotide for the M5 muscarinic receptor infused near dopamine cells. *J. Neurosci.* 20, 8861–8867.
- Yeomans, J.S., Forster, G., and Blaha, C. (2001). M5 muscarinic receptors are needed for slow activation of dopamine neurons and for rewarding brain stimulation. *Life Sci.* 68, 2449–2456.
- You, Z.-B., Tzschentke, T.M., Brodin, E., and Wise, R.A. (1998). Electrical stimulation of the prefrontal cortex increases cholecystokinin, glutamate, and dopamine release in the nucleus accumbens: an *in vivo* microdialysis study in freely moving rats. *J. Neurosci.* 18, 6492–6500.
- Zangen, A., Ikemo, S., and Wise, R.A. (2002). Rewarding and psychomotor stimulant effects of endomorphin-1: Anterior-posterior differences within the ventral tegmental area and lack of effect in nucleus accumbens. *J. Neurosci.*, in press.