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You are what you eat: influence of type and amount of food consumed on central dopamine systems and the behavioral effects of direct- and indirect-acting dopamine receptor agonists

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Abstract

The important role of dopamine (DA) in mediating feeding behavior and the positive reinforcing effects of some drugs is well recognized. Less widely studied is how feeding conditions might impact the sensitivity of drugs acting on DA systems. Food restriction, for example, has often been the focus of aging and longevity studies; however, other studies have demonstrated that mild food restriction markedly increases sensitivity to direct- and indirect-acting DA receptor agonists. Moreover, it is becoming clear that not only the amount of food, but the type of food, is an important factor in modifying the effects of drugs. Given the increased consumption of high fat and sugary foods, studies are exploring how consumption of highly palatable food impacts DA neurochemistry and the effects of drugs acting on these systems. For example, eating high fat chow increases sensitivity to some behavioral effects of direct- as well as indirect-acting DA receptor agonists. A compelling mechanistic possibility is that the central DA pathways that mediate the effects of some drugs are regulated by one or more of the endocrine hormones (e.g. insulin) that undergo marked changes during food restriction or after consuming high fat or sugary foods. Although traditionally recognized as an important signaling molecule in regulating energy homeostasis, insulin can also regulate DA neurochemistry. Because direct- and indirect-acting DA receptor drugs are used therapeutically and some are abused, a better understanding of how food intake impacts response to these drugs would likely facilitate improved treatment of clinical disorders and provide information that would be relevant to the causes of vulnerability to abuse drugs.

Keywords

feeding condition; food restriction; high fat chow; DA systems; direct-acting DA receptor agonist; indirect-acting DA receptor agonist

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1. Dopamine systems

Dopamine (DA) is the predominant catecholamine neurotransmitter in the mammalian brain, where it controls a variety of physiological functions including locomotor activity, cognition, emotion, reward, sleep, and food intake. DA also exerts a role in the periphery as a modulator of cardiovascular function, hormone secretion, renal function, and gastrointestinal motility. Since the discovery of DA more than 50 years ago (Carlsson et al., 1957), DA systems have been the focus of much research. Furthermore, a variety of human disorders are thought to be due, at least in part, to dysfunction in DA systems, including Parkinson's disease. Abnormal DA signaling is also thought to play a role in attention deficit hyperactivity disorder (ADHD), Tourette's syndrome, and drug abuse (Koob and Volkow, 2010; Mink, 2006; Swanson et al., 2007).

Four major dopaminergic pathways have been identified in the mammalian brain: the nigrostriatal, mesolimbic, mesocortical, and tuberoinfundibular systems (Anden et al., 1964; Dahlstroem and Fuxe, 1964). DA synthesis originates from tyrosine, and its rate-limiting step is the conversion of L-tyrosine to L-dihydroxyphenylalanine (L-DOPA) by the enzyme tyrosine hydroxylase. L-DOPA is subsequently converted to DA by the enzyme L-aromatic amino acid decarboxylase. In DA neurons, DA is transported from the cytoplasm to specialized storage vesicles via the synaptic vesicular monoamine transporter. On the other hand, the plasma membrane DA transporter (DAT), located on DA neurons, transports DA in and out of the terminal depending on the existing concentration gradient and other factors (Amara and Kuhar, 1993). DAT is the primary mechanism of DA clearance from the synapse; however, other enzymatic pathways contribute to DA metabolism. The main metabolites of DA in the central nervous system are homovanillic acid (HVA), dihydroxyphenylacetic acid (DOPAC), and a small amount of 3-methoxytyramine (3-MT). DA is converted to DOPAC, either intraneuronally or extraneuronally, by monoamine oxidase whereas the conversion of DA to HVA occurs extraneuronally because of the extracellular location of the enzyme catechol-*O*-methyltransferase (for further reading, see Feldman et al., 1997). In rats, DOPAC is the major metabolite of DA, whereas in human and non-human primates, the major brain metabolite is HVA (Westerink, 1985). Alterations of DA metabolites can occur from drug treatment (e.g. antipsychotics) as well as certain disorders (e.g. Parkinson's disease). In rats, for example, administration of a DA receptor agonist decreases, while administration of a DA receptor antagonist increases, DA cell activity, turnover, degradation, and metabolite concentrations (Imperato and Di Chiara, 1985).

The discovery that DA receptor agonists and the DA precursor L-DOPA (which is administered to compensate for the lack of endogenous DA) have beneficial effects in Parkinson's patients, provided clear evidence that DA systems are important pharmacological targets. Two important sites of action in DA systems are DA receptors and the DAT. DA receptors are classified into two subfamilies, D1- and D2-like receptors (Brown and Makman, 1972; Kebabian and Calne, 1979), based on their pharmacological and functional properties. Furthermore, based on the genes encoding them, the D1-like receptors are classified as D1 and D5 receptors (Sunahara et al., 1990, 1991), whereas the D2-like receptors are classified as D2, D3, and D4 (Sokoloff et al., 1990). DA D1 and D5 receptors are positively coupled to adenylyl cyclase by the G protein G_s , whereas D2, D3, and D4 receptors inhibit this enzyme by coupling to $G_{i/o}$. The D1-like and D2-like receptor mRNAs are present in all DA-containing regions of the rat brain (Meador-Woodruff, 1994). Although these DA receptors appear to have overlapping distributions, there are some differences in their anatomical locations. For example, high levels of D2, but not D1, mRNA are detected in the substantia nigra and ventral tegmental area. Furthermore, in rats D3 receptors display a much more restricted, limbic pattern of distribution compared with that

of D2 receptors (Levesque et al., 1992). Some agonists and antagonists that act directly at DA receptors are used therapeutically. For example, all antipsychotics and anti-Parkinson drugs act predominantly through the D2-like family of DA receptors. In rats, agonists and antagonists acting directly at D2 and D3 receptors can induce a number of effects including the following: yawning (Baladi and France, 2009; Collins et al., 2005), hypothermia (Chaperon et al., 2003; Collins et al., 2007), discriminative stimulus effects (Katz and Alling, 2000; Kleven and Koek, 1997), catalepsy (Hauber et al., 2001), and penile erection (Depoortère et al., 2009).

Other drugs act indirectly at DA receptors as either reuptake blockers (e.g. cocaine) or releasers (e.g. amphetamine) of DA. Although these drugs are also used therapeutically (e.g. narcolepsy, ADHD), they have a high potential for being abused. For example, cocaine binds to DAT (as well as other monoamine transporters) and blocks the reuptake of DA into presynaptic terminals (Heikkila et al., 1975; Koe, 1976; Reith et al., 1986) while amphetamine increases DA release through reversal of DAT activity (Jones et al., 1999; Liang and Rutledge, 1982). Blocking reuptake or promoting release of DA enhances extracellular concentrations of DA (Kalivas and Duffy, 1990; Weiss et al., 1992) that binds to various DA receptors. A number of chemically diverse DA reuptake inhibitors, DA releasers, and direct-acting DA receptor agonists can mimic the behavioral (e.g. discriminative stimulus) effects of drugs like cocaine and some DA receptor antagonists attenuate the effects of cocaine (Acri et al., 1995; Caine and Koob, 1993; Spealman 1996; Witkin et al., 1991). Although the relative contribution of each receptor subtype to the effects of cocaine is not fully known, D2 and D3 receptors are thought to mediate many of the behavioral effects of cocaine (Acri et al., 1995; Caine and Koob, 1993; Sinnott et al., 1999; Spealman, 1996). A number of studies indicate an important role for DA in the effects of cocaine; however, and in contrast to direct-acting DA receptor agonists, other neurotransmitter systems are thought to play a role in mediating the effects of cocaine, including norepinephrine (Johanson and Barrett, 1993) and serotonin (Cunningham and Callahan, 1991) systems.

A growing body of evidence indicates the importance of D2 and D3 receptors in the abuse-related and therapeutic effects of direct- and indirect-acting DA receptor drugs. Furthermore, there is considerable interest in developing selective D3 receptor ligands because they have a unique anatomical distribution (i.e. relative to D2 receptors); this has prompted speculation that antipsychotic drugs (i.e. DA receptor antagonists) acting at D3 receptors might not induce the extrapyramidal side effects that develop after repeated treatment with antagonists acting at D2 receptors and that anti-Parkinson drugs (i.e. agonists) acting at D3 receptors might have neuroprotective effects (See Heidbreder and Newman, 2010; Joyce, 2001). Given the well-established role of DA receptor subtypes in various disease states and in drug abuse, it is important to understand factors that might alter sensitivity to the behavioral effects of drugs acting directly or indirectly at DA receptors. These factors that can impact individual differences in response to therapeutic drugs and in vulnerability to substance abuse are not fully understood and include age (Kostrzewa et al. 1991; Zakharova et al., 2009), behavioral and drug history (Collins and Woods, 2009; Nader and Mach, 1996), and genetics; an additional factor that has not been fully explored, but which has been shown to impact DA neurochemistry and the effects of drugs acting on DA systems, is feeding condition. Here we review the relationship between feeding condition and DA neurochemistry as well as feeding condition and the actions of drugs acting on DA systems.

2. Feeding condition and drugs: convergence on DA systems

Eating disorders show high co-morbidity with substance abuse (Holderness et al., 1994; Krahn, 1991; Piran and Robinson, 2006) and some food and drugs can activate common DA

systems (Di Chiara and Imperato, 1988; Wise and Rompre, 1989). DA mechanisms mediate, in part, the positive reinforcing effects of some drugs (Di Chiara and Imperato, 1988; Wise and Rompre, 1989) and food (Hernandez and Hoebel, 1988; Wise, 2006). For example, many drugs that are abused (e.g. cocaine, nicotine, opioids) increase extracellular concentrations of DA in rats, primarily in the nucleus accumbens (Di Chiara and Imperato, 1988). Similarly, eating certain foods (e.g. standard laboratory chow) increases extracellular DA in the nucleus accumbens of rats (Hernandez and Hoebel, 1988). A number of studies have examined how drugs acting on DA systems impact feeding behavior (Clifton and Kennett, 2006; Heffner et al., 1977; Palmiter, 2007; Palmiter, 2008; Salamone et al., 2003; Terry et al., 1995). For example, when DA levels are depleted, animals stop feeding and might starve, whereas when DA levels are restored (i.e. treatment with L-DOPA), feeding behavior returns to normal (Sotak et al., 2005; Szczepka et al., 2001). Studies addressing central nervous system regulation of food intake are reviewed elsewhere in this journal edition and are beyond the scope of this contribution (also see Morton et al., 2006; Schwartz et al., 2000); however, because food and drugs converge on DA systems, there is a growing interest in and literature on the impact of different feeding conditions on sensitivity to drugs acting on DA systems (see Tables 1 and 2), which is the focus of this review.

3. Impact of feeding condition on drugs acting on DA systems

3.1 Food restriction and direct-acting DA receptor agonists

One approach to examine whether feeding condition alters DA receptors, particularly D2 and D3 receptors, is to study the effects of drugs that bind directly to these receptors. However, interpretation of results obtained with direct-acting drugs can be complicated by the fact that many of the direct-acting DA receptor agonists and antagonists that are available for laboratory studies bind to (and in the case of agonists have efficacy at) more than one type of DA receptor (e.g., D2 and D3 receptors). For example, food restriction increases the locomotor effects (Carr et al., 2003; Collins et al., 2008) and yawning (Baladi and France, 2009; Collins et al., 2008) produced by agonists that act at both D2 and D3 receptors. However, the effects of food restriction on DA (D2 and D3 receptor-mediated) agonist-induced yawning can be reversed by a D2 receptor selective antagonist, indicating that increased sensitivity to agonists is mediated by D2 receptors (Collins et al., 2008). Moreover, it has been reported that food restriction increases sensitivity to DA receptor agonist-induced hypothermia, an effect that is thought to be mediated by D2 receptors (Collins et al., 2008). Many studies conducted with food-restricted rats confirm that the discriminative stimulus effects of several different direct-acting DA receptor agonists that bind to both D3 and D2 receptors are mediated through D2 receptors (Appel et al., 1988; Baker et al., 1999; Bristow et al., 1998; Christian et al., 2001; Katz and Alling, 2000; Kleven and Koek, 1997; Koffarnus et al., 2009; Millan et al., 2000, 2007). However, using an avoidance/escape procedure to maintain responding (modified after Shannon and Holtzman, 1976) rather than food (i.e. rats had free access to food since lever pressing was not maintained by food presentation), it was recently demonstrated that in free-feeding rats the discriminative stimulus effects of some of the same direct-acting DA receptor agonists (e.g. quinpirole) are mediated by D3 and not D2 receptors (Baladi et al., 2010). Thus, food restriction can modify both the potency of direct-acting D2/D3 receptor agonists (see Table 1) as well as the relative contribution of D2 and D3 receptors in mediating the effects of these drugs. The notion that feeding condition can change the relative contribution of DA receptors to the same effect of the same drug might be relevant to understanding individual differences in therapeutic response to DA receptor agonists.

3.2 Food restriction and indirect-acting DA receptor agonists

Indirect-acting DA receptor agonists do not directly bind to DA receptors, but rather, their actions are mediated through stimulation of DA receptors via an increased synaptic concentration of DA. Some indirect-acting DA receptor agonists have actions on non-DA systems (Cunningham and Callahan, 1991; Johanson and Barrett, 1993; Reith et al., 1997) and those actions might also be influenced by feeding condition. Nevertheless, because food restriction modifies the effects of agonists acting directly at DA receptors, it might be expected that food restriction would also modify the effects of indirect-acting DA receptor agonists. In fact, food restriction increases the locomotor effects of indirect-acting DA receptor agonists such as cocaine (Deroche et al., 1993; Stamp et al., 2008). One widely studied behavioral phenomenon, indicative of a functional association between mechanisms regulating food and drug intake, is the enhancement of drug self-administration by food restriction. For example, when human subjects already in a healthy weight range were reduced to 75% of their body weight, cigarette smoking and coffee drinking increased markedly (Franklin et al., 1948). Laboratory studies with several classes of drugs (e.g. stimulants and opioids), species (e.g. rats and rhesus monkeys), and routes of self-administration (e.g. oral and i.v.) have confirmed and extended this relationship between food restriction and drug reinforcement. For example, food restriction increases self-administration of several drugs, including amphetamine (Takahashi et al., 1978), heroin (Oei et al., 1980), and cocaine (Carroll et al., 1981). Furthermore, increased self-administration is evident within 8 hours of food being removed from the chamber and self-administration returns to normal (lower) levels almost immediately when rats are given free access to food (Carroll et al., 1981). An 8-hour delay from food restriction to increased self-administration suggests that time dependent physiological changes, rather than simply the absence of food, might be necessary for increased drug self-administration (Carroll and Meisch, 1980). Food restriction also increases amphetamine-induced conditioned place preference and locomotor activity (Stuber et al., 2002). Although feeding condition can impact the discriminative stimulus effects of direct-acting DA receptor agonists (Baladi and France, 2010; Baladi et al., 2011), it is unclear whether food restriction modifies the discriminative stimulus effects of indirect-acting DA receptor agonists. However, ongoing studies suggest that the ability of direct-acting D2/D3 receptor agonists to mimic the discriminative stimulus effects of cocaine differs between free-feeding and food-restricted rats (Fig. 1; Baladi et al., unpublished results). For example, the direct-acting D2/D3 receptor agonists lisuride and quinpirole are less effective to produce responding on the cocaine-associated lever in food-restricted, as compared with free-feeding, rats (Fig.1). It might be that the relative selectivity of these drugs for D2 and D3 receptors impacts their ability to mimic the discriminative stimulus effects of the indirect-acting DA receptor agonist cocaine. Thus, food restriction appears to modify the potency of indirect-acting DA receptor agonists (see Table 1) as well as the relative contribution of different DA receptors (D2 and D3) in mediating the effects of these drugs.

3.3 High fat chow and direct-acting DA receptor agonists

While it is clear that the amount of food eaten (i.e. food restriction) can impact the effects of drugs acting on DA systems, much less is known about whether the content of food alters the effects of drugs acting on DA systems. However, recent studies suggest that eating high fat chow impacts the sensitivity of rats to the behavioral effects of direct-acting D2/D3 receptor agonists. For example, rats eating high fat chow are more sensitive to quinpirole-induced discriminative stimulus effects and yawning (D2 and D3 receptor-mediated; Baladi and France, 2010) as compared with rats eating standard laboratory chow. In addition, the adult offspring of dams fed a high fat diet during gestation are more sensitive to quinpirole-induced locomotor activity (Naef et al., 2011).

Thus, it appears that both the amount of food (i.e. free feeding or food restricted) and type of food (i.e. standard or high fat) contribute to changes in sensitivity to drugs acting on DA systems. A recent study further examined how type of food and body weight changes influence the behavioral effects of direct-acting DA receptor agonists (i.e. quinpirole) by systematically varying body weight (increasing, decreasing, or staying the same). Rats ate either standard (5.7% fat) or high fat (34.3%) chow and body weights were matched for separate groups of rats eating different chows (Baladi et al., 2011). Eating high fat chow, even when food intake was adjusted so that body weight gain was normal, increased the sensitivity of rats to D3 and D2 receptor-mediated effects of quinpirole. That is, the critical factor in whether the effects of quinpirole were altered appeared to be the consumption of high fat chow and not necessarily increased body weight. On the other hand, regardless of the type of chow that rats ate, food restriction (such that body weight decreased or remained the same) enhanced the sensitivity of rats to D2 receptor-mediated effects of quinpirole. Therefore, depending on the condition, the type of chow or body weight change can impact sensitivity to direct-acting DA receptor agonists.

3.4 High fat chow and indirect-acting DA receptor agonists

Although intriguing data are emerging regarding the effects of eating high fat chow on the actions of direct-acting DA receptor agonists, much less is known regarding the effects of eating high fat chow on the actions of indirect-acting DA receptor agonists. Several studies have examined altered preference for non-drug reinforcers in animals eating highly palatable food (e.g. food, sugar; Corwin et al., 2011; Cottone et al., 2008; Johnson and Kenny, 2010). For example, rats eating high fat chow respond less for a sucrose pellet (Davis et al., 2008). However, when rats are given intermittent access to highly palatable substances (e.g. sucrose, high fat chow), intake during a limited access period escalates across several weeks and becomes significantly greater as compared with rats given daily access to highly palatable substances (Corwin et al., 2011). Others have examined interactions between genetically obese animal strains that eat high fat chow and sensitivity to the effects of cocaine; for example, eating high fat chow increases sensitivity to cocaine-induced conditioned place preference in obese-resistant, but not obese-prone, rats (Thanos et al., 2010).

Eating high fat chow (in outbred rats) reportedly decreases sensitivity to some effects of amphetamine (i.e. conditioned place preference; Davis et al., 2008) and cocaine (i.e. acquisition of self-administration; Wellman et al., 2007) in studies that examined effects of a single dose. However, when a full range of doses was examined, eating high fat chow significantly enhanced the sensitization that develops to repeated intermittent administration of methamphetamine (i.e. locomotor activity; McGuire et al., 2011). It is unclear to what extent feeding conditions, such as eating high fat chow, differentially modify sensitivity to indirect-acting DA receptor agonists with different mechanisms of action (Glick et al., 1987), although further studies appear warranted in light of the profound effects of different feeding conditions on brain neurochemistry and on the effects of direct-acting DA receptor agonists. These results indicate that, in general, food restriction and eating high fat chow increase sensitivity to drugs acting either indirectly or directly at DA receptors (see Tables 1 and 2); moreover, food restriction appears to selectively increase sensitivity at D2 receptors while eating high fat chow increases sensitivity at both D3 and D2 receptors (Baladi et al., 2011; Collins et al., 2008).

3.5 Other highly palatable substances and direct- and indirect-acting DA receptor agonists

Although the majority of this review focuses on the impact of feeding conditions, such as food restriction and eating high fat chow, on sensitivity to drugs acting on DA systems, there is evidence that other dietary conditions, such as drinking sucrose, can alter the effects of

these drugs (Avena and Hoebel, 2003; Foley et al., 2006; Gosnell, 2005). For example, consuming sucrose enhances sensitization to the locomotor effects of direct-acting DA receptor agonists such as quinpirole (Foley et al., 2006) and indirect-acting DA receptor agonists such as cocaine (Gosnell, 2005). Given that many drugs (therapeutics and drugs of abuse) act on DA systems and that consumption of highly palatable foods (sucrose and high fat) varies widely among individuals and is increasing worldwide (Lustig et al., 2012; Misra et al., 2010; Popkin and Nielsen, 2003), it might be particularly useful to examine the short and long term consequences of eating different highly palatable foods on sensitivity to drugs. As mentioned previously, it appears that simply consuming highly palatable foods (eating high fat chow but not exceeding normal body weight) can profoundly impact DA neurochemistry and the effects of drugs acting on DA systems (Baladi et al., 2011; Corwin et al., 2011).

4. Feeding condition and drugs acting on non-DA neurotransmitter systems

Although DA mechanisms play an important role in mediating the positive reinforcing effects of many drugs of abuse (Carboni et al., 2000; Gratton et al., 1994; Wise and Rompre, 1989) and food (Carr, 2007; Wise, 2006), other neurochemical systems, including opioid, serotonin, and cannabinoid, also are thought to play a role in motivated behavior (Koob, 1992; Reith et al., 1997). Just as feeding conditions can dramatically impact DA systems, it is becoming increasingly clear that feeding conditions can also impact other neurochemical systems that play a role in drug and food reinforcement. For example, access to highly palatable substances (e.g. sucrose, fat) increases the antinociceptive effects of morphine (Bergmann et al., 1985; Kanarek et al., 2000; Klein et al., 1988). Furthermore, food restriction decreases sensitivity of rats to some behavioral effects of direct- and indirect-acting serotonin receptor agonists (France et al., 2009; Li and France, 2008) while eating high fat chow increases the sensitivity of rats to some effects of direct-acting serotonin receptor agonists (Li et al., 2011). Finally, eating high fat chow decreases sensitivity to the cataleptic effects of the cannabinoid receptor agonist delta-9-tetrahydrocannabinol (Wiley et al., 2011). Taken together, these data suggest that feeding conditions can impact non-DA neurotransmitter systems and possibly, the therapeutic and/or abuse-related effects (e.g. opioid drugs for treatment of pain; serotonin drugs for treatment of depression) of drugs acting on these systems. The relative paucity of information regarding the impact of feeding condition on the actions of drugs acting on non-DA systems underscores the need for further investigation of these neurotransmitter systems under different dietary conditions.

5. Potential mechanisms

There are a multitude of mechanisms that might account for how changes in diet modify the behavioral effects of drugs acting either indirectly and directly at DA receptors. Although not a comprehensive list, some of the potential mechanisms that might contribute to diet-induced changes in drug action include pharmacokinetics, hypothalamic-pituitary-adrenal axis activity, DA neurochemistry, and hormones.

5.1 Feeding and pharmacokinetics

Feeding conditions might alter pharmacokinetics and bioavailability of drugs. For example, food restriction can alter hepatic drug-metabolizing enzyme activity (Ma et al., 1989), decrease drug binding to plasma protein (Gugler et al., 1974), and increase permeability of the blood-brain barrier (Pollay and Stevens, 1980). However, the fact that food restriction alters drug sensitivity even when drugs are administered directly into the brain suggests that the enhanced sensitivity is unlikely due to pharmacokinetic factors (Carr et al., 2003).

Moreover, male and female rats that vary significantly in body weight and in fat content show remarkably similar pharmacokinetic profiles for some drugs that act on DA systems (e.g. cocaine; Bowman et al., 1999). If diet-induced changes in sensitivity to drugs were due to pharmacokinetics exclusively, then all effects of a particular drug should be altered in a similar manner. Dopamine agonist-induced yawning and hypothermia are both thought to be mediated in the central nervous system (Dourish and Hutson, 1985; Nunes et al., 1991); however, despite significant changes in sensitivity to quinpirole-induced yawning in rats that are food restricted or in those eating high fat chow, quinpirole-induced hypothermia was unchanged across all groups of rats (Baladi et al., 2011). Differential effects of diet on quinpirole-induced yawning and hypothermia might reflect different populations of DA receptors mediating these effects (the paraventricular nucleus of the hypothalamus mediating yawning [Arigolas and Melis, 1998] and the anterior hypothalamus/preoptic area mediating hypothermia [Lin et al., 1982]) and/or other compensatory mechanisms regulating body temperature.

5.2 Feeding and the hypothalamic-pituitary-adrenal axis

Food restriction might also modify activity of the hypothalamic-pituitary-adrenal axis (e.g. steroid hormones) in a manner that alters sensitivity to drugs. For example, food restriction increases circulating concentrations of steroid hormones such as corticosterone (Stamp et al., 2008) and corticosterone concentration is positively correlated with self-administration of amphetamine and cocaine (Goeders and Guerin, 1996; Piazza et al., 1991). Other studies showed that pharmacological blockade of corticosterone reverses the effects of food restriction on increased sensitivity to cocaine (Marinelli et al., 1996). However, inhibitors of corticosterone synthesis do not consistently block food restriction-induced increases in sensitivity to drugs acting on DA systems (Campbell and Carroll, 2001; Carroll et al., 2001; Carr, 2002). Furthermore, it appears as though food restriction-induced increases in corticosterone levels do not unanimously predict increased sensitivity to drugs such as methamphetamine (Sharpe et al., 2011), an indirect-acting DA receptor agonist. At least for some steroid hormones, the time course of hormonal changes do not predict the time course of changes in sensitivity to drugs; for example, altered hormonal status from a period of food restriction lasts considerably longer than changes in sensitivity to drug, which return to normal within 1 week of resuming normal eating conditions (Carr, 2002).

5.3 Feeding and DA neurochemistry

Food restriction has been shown to decrease extracellular DA concentration in the nucleus accumbens (Pothos et al., 1995), increase D2 receptor binding (Thanos et al., 2008), and increase coupling between D2 receptors and G proteins (Carr, 2002). Some have reported decreases (ventral tegmental area/substantia nigra pars compacta; Patterson et al., 1998) while others have reported increases (ventral tegmental area; Lindblom et al., 2006) in DAT mRNA levels in food restricted rats. In terms of DAT activity, food restriction significantly decreases DA clearance rate (Patterson et al., 1998; Sevak et al., 2008). Finally, in food-restricted rats, amphetamine-stimulated DA release is reported to be either increased (Pothos et al., 1995) or unchanged (Stuber et al., 2002), as compared with rats that are not food restricted. These mixed results among laboratories might be due to differences in experimental design (e.g. food restriction protocol), experimental procedure, and the particular drug as well as doses that were studied.

Rats eating high fat chow have decreased extracellular DA in the nucleus accumbens (Rada et al., 2010), increased D2 receptor binding (South and Huang, 2008), and decreased DA transporter density (Huang et al., 2006); however, others have reported decreased D2 receptor binding in obese rats (Johnson and Kenny, 2010). Eating high fat chow also

decreases DA release (York et al., 2010), DA clearance rate (Speed et al., 2011; Baladi et al., unpublished results), and DA turnover (Davis et al., 2008).

5.4 Feeding and hormones: focus on insulin

The underlying mechanism(s) that mediates the effects of feeding condition on DA neurochemistry and on sensitivity to drugs is unclear although several studies implicate hormones that are known to be impacted by feeding condition (Carr, 2002; Marinelli and Piazza, 2002). For example, hormones like insulin, leptin and ghrelin, that are typically studied as hormonal inputs to homeostatic metabolic systems (Figlewicz, 2003), also directly affect DA systems (Daws et al., 2011; Niswender et al., 2011). For example, leptin and ghrelin receptors are expressed in the ventral tegmental area and double-label studies have demonstrated co-expression of these receptors with tyrosine hydroxylase, a marker of DA neurons (Abizaid et al., 2006; Hommel et al., 2006; Fulton et al., 2006). In addition, Fulton and colleagues (Fulton et al., 2006) demonstrated that leptin increased the response of mice to amphetamine-stimulated locomotion. Insulin acts on insulin receptors as well as insulin-like growth factor receptors that are widely distributed in the brain, including the cerebral cortex, limbic system, and hypothalamus (Havrankova et al., 1981; Marks and Eastman, 1990; Zahniser et al., 1984). The downstream effects of insulin include activation of phosphoinositide 3-kinases and protein kinase B (i.e. Akt; Taha and Klip, 1999). Insulin receptors are expressed in brain regions that are rich in DA neurons, receptors, and transporters; for example, insulin receptors are coexpressed with tyrosine hydroxylase (Figlewicz et al., 2003), suggesting a functional interaction between insulin and DA systems. In fact, changes in circulating insulin can markedly affect synthesis, turnover, and receptor-mediated effects of DA (Kwok and Juorio, 1986; Lim et al., 1994; Lozovsky et al., 1981; Saller, 1984). Several studies have demonstrated that insulin, via the phosphoinositide 3-kinase/Akt signaling pathway (Williams et al., 2007), regulates the expression and activity of DAT as well as sensitivity to drugs acting on DA systems. For example, acute administration of insulin enhances expression and activity of DAT (Carvelli et al., 2002; Figlewicz et al., 1994). On the other hand, rats made hypoinsulinemic (e.g. administration of streptozotocin or food restriction) have decreased mRNA expression and DAT activity (Owens et al., 2005; Patterson et al., 1998; Sevak et al., 2008) and insulin replacement restores normal DAT activity (Patterson et al., 1998; Williams et al., 2007). Streptozotocin-treated rats also have increased sensitivity to indirect- and direct-acting DA receptor agonists (i.e. amphetamine and quinpirole, respectively; Owens et al., 2005; Sevak et al., 2007a). Interestingly, insulin and drugs acting on DA systems might regulate DA systems through the same site/pathway. For example, both insulin and amphetamine can increase expression and/or activity of D2 receptors in brain (Lim et al., 1994; Owens et al., in press; Seeman et al., 2002; Sumiyoshi et al., 1997) and D2 receptors regulate the rate of DA uptake in brain (Cass and Gerhardt, 1994; Dickinson et al., 1999; Meiergerd et al., 1993; Owens et al., in press). Moreover, administration of amphetamine restores normal DA clearance rate in streptozotocin-treated rats (Owens et al., 2005) and this effect is mediated through D2 receptors (Owens et al., in press; Sevak et al., 2007b). Collectively these results strongly implicate insulin as playing a major role in regulating the activity of DA systems in brain.

Food restriction and eating high fat chow can have opposite effects on levels of circulating insulin. For example, food restriction decreases circulating insulin (Carr, 1996; Kinzig et al., 2009) while acute consumption of highly palatable foods (e.g. high fat chow) can increase circulating insulin (Shiraeve et al., 2009). However, sustained consumption of high fat chow and resulting high levels of circulating insulin can lead to insulin resistance (Baladi et al., 2011; Davidson and Garvey, 1993; Morris et al., 2011; Schemmel et al., 1982; Wilkes et al., 1998) and decreased insulin signaling. Given the growing evidence that DA systems are modulated by insulin signaling (Daws et al., 2011; Niswender et al., 2011) it is likely that,

regardless of the manner in which insulin signaling is decreased, shifts in the sensitivity of rats to drugs acting on DA systems will be similar. For example, insulin receptors are expressed on DA neurons and manipulation of insulin levels can affect both the activity and expression of DAT. Both food restriction and eating high fat chow, as well as experimentally induced diabetes, decrease DAT expression and function (Baladi et al., unpublished results; Patterson et al., 1998; Sevak et al., 2008; South and Huang, 2008; Speed et al., 2011; Williams et al., 2007). Unlike DAT, less is known about the effect of blunted insulin signaling on dopamine receptor expression and function, perhaps not surprisingly given the complexities of deciphering actions of pre- versus post-synaptic DA receptors, as well as the contributions from each DA receptor subtype. Activation of DA receptors is contingent, in part, on the amount of DA in the extracellular fluid, which is dynamically regulated by the balance between DA release and its uptake by DAT, as well as other low-affinity, but high-capacity transporters for DA including the norepinephrine transporter (NET; Carboni and Silvagni, 2004), organic cation transporters (OCTs; Koepsell et al., 2007) and the plasma membrane monoamine transporter (PMAT; Duan and Wang, 2010). Few studies have investigated the consequence of reduced insulin signaling on extracellular DA and the results are mixed (Murzi et al., 1996; Ohtani et al., 1997; Rada et al., 2010). This apparent discord is likely due, in part, to differences in the way in which insulin signaling is manipulated (e.g. feeding paradigm and duration, induction of diabetes, species, brain region studied, etc). Nevertheless, while decreased DAT activity (i.e. DA clearance) might initially increase extracellular DA concentration, long term suppression of insulin signaling might produce adaptive changes in other mechanisms controlling DA neurotransmission, such as a decrease in stimulated DA release, and/or increased activity of non-DAT transporters for DA.

Although either mechanism could lead to a reduction in extracellular DA and compensatory upregulation of post-synaptic DA receptors, in terms of DA release, amphetamine stimulated DA release is markedly attenuated in diabetic and insulin-resistant animals (Williams et al., 2007; Speed et al., 2011). Since amphetamine stimulates DA release via reverse transport through the DAT, this result is consistent with reduced DAT expression on the plasma membrane of nerve terminals. These results are also consistent with the view that DA stores in nerve terminals may be depleted as a result of hypoinsulinemia or insulin resistance. Early studies indicate that DA release evoked by indirect dopamine agonists, such as amphetamine, come from newly synthesized rather than vesicular pools of DA, (Nielsen et al., 1983; Parker and Cubeddu, 1986a; Parker and Cubeddu, 1986b). However, more recent studies by Sabol and Seiden (1998) and Jones et al., (1998) reveal that amphetamine causes the release of both newly synthesized, cytoplasmic pools and vesicular pools of DA. Moreover, there is now evidence suggesting that heterogeneity exists among vesicular DA pools; for example, some vesicular pools are reserpine-sensitive, while others are relatively insensitive (Wang et al., 2011; Yavich and MacDonald, 2000). Based on this literature it is reasonable to speculate that prolonged blunting of insulin signaling might produce an overall reduction in subpopulations of releasable vesicular pools of DA, as well as reductions in newly synthesized pools.

In terms of mechanisms regulating DA uptake from extracellular fluid, there is evidence suggesting that NET responds to blunted insulin signaling in the opposite way to DAT; that is, NET plasma membrane expression and function increases when insulin signaling is impaired (Roberston, et al., 2010). Likewise, the serotonin transporter (SERT) also appears to increase its activity in hypoinsulinemic rats (France et al., 2009). Both NET and SERT can take up DA (Carboni and Silvagni, 2004; Larsen et al., 2011), therefore hyperactivity of non-DAT transporters may lead to an overall reduction in extracellular DA.

It is clear that the precise mechanisms leading to increased sensitivity to the behavioral effects of DA acting drugs in animals with reduced insulin signaling remain to be elucidated. We propose two ways in which this could occur: 1) reduced cytoplasmic and/or vesicular stores of DA resulting in less DA available for release into the extracellular domain; and 2) enhanced DA uptake from extracellular fluid via non-DAT transporters. Either way, the predicted effect would be an overall reduction in extracellular DA following sustained inhibition of insulin signaling and a compensatory increase in the expression (sensitivity) of post-synaptic DA receptors. While these mechanisms remain to be empirically tested, they provide ways in which diverse eating conditions (food restriction, high fat chow), via blunted insulin signaling, can produce similar effects on DA levels in the extracellular fluid and similar increases in sensitivity to drugs acting on DA systems.

6. Summary

While DA has long been recognized as an important mediator of feeding behavior and the positive reinforcing effects of drugs as well as other stimuli, the findings presented in this review highlight the complex interaction among feeding condition, drug action, and DA systems. In general, food restriction (see Table 1) increases sensitivity to behavioral effects of direct- and indirect-acting DA receptor agonists. Moreover, the majority of studies have focused on drugs acting at D2 and D3 DA receptor subtypes and these receptors are thought to be important for both the therapeutic and abuse-related effects of several drugs. Despite the fact that D2 and D3 receptors share similar sequence homology and signal transduction pathways (Cho et al., 2010), food restriction appears to increase sensitivity at D2, but not D3, receptors (Baladi et al., 2010; Carr et al., 2003; Collins et al., 2008). Both the amount and type of food are important determinants of sensitivity to direct-acting DA receptor agonists. The data are less clear with indirect-acting DA receptor agonists with some studies reporting decreases and others reporting increases in sensitivity to drugs in rats eating high fat chow (see Table 2). Nevertheless, it appears as though eating high fat chow can increase sensitivity to both D2 and D3 receptor mediated drug effects (Baladi et al., 2011). Furthermore, robust changes in sensitivity to drugs acting on DA systems can occur in the absence of body weight differences, highlighting the fact that consumption of fat, and not being “fat”, appears to be the critical determinant for altering drug effects. Finally, a growing body of literature obtained in animals eating different amounts and types of chow and in studies where insulin was directly manipulated (e.g. streptozotocin) suggest that by affecting the dynamics of DA neurochemistry, insulin might influence changes in sensitivity to the behavioral effects of direct- and indirect-acting DA receptor agonists.

There is much still to be learned regarding interactions among feeding conditions, sensitivity to drugs, and DA systems. This review focuses on food restriction and eating high fat chow on sensitivity to direct- and indirect-acting DA receptor agonists although there is evidence to suggest that feeding conditions can profoundly affect other neurochemical systems and the actions of drugs acting on those systems (e.g., France et al., 2009).

7. Relevance

Some of the same neurotransmitter systems (e.g. DA) that mediate the effects of therapeutic drugs and drugs of abuse are also thought to be altered in some psychopathologies. Thus, nutritional factors of the type discussed in this review might contribute both to the etiology of psychopathology (e.g. substance abuse) and to the effectiveness of drugs used to treat those psychopathologies, thereby affecting therapeutic outcome or vulnerability to abuse drugs. The potential importance of understanding relationships among food intake, psychiatric disorders, and the effects of drugs is highlighted by the following: 1) there is a worldwide obesity epidemic, and obesity is correlated with decreased responsiveness to

some drugs (i.e. anti-depressants; Khan et al., 2007; Kloiber et al., 2007); 2) diabetes is increasing worldwide, and insulin is known to regulate DA systems that mediate the effects of many therapeutic and abused drugs (Sevak et al., 2007a); 3) food restriction in certain populations is associated with decreased sensitivity to some therapeutic drugs (e.g. anorexia; Kaye et al., 1998); and 4) diet-induced changes in DA systems can persist for a very long time and might predispose individuals to an altered responsiveness to drugs for an extended period (Frank et al., 2005; Naef et al., 2008, 2011). Furthermore, there are comorbidities between feeding behavior and psychiatric disorders such as eating disorders and drug abuse (Franko et al., 2008; Wiederman and Pryor, 1996), diabetes and schizophrenia (Dixon et al., 2000; Mukherjee et al., 1996), and obesity and depression (Faith et al., 2002; McElroy et al., 2004; Simon et al., 2006). Taken together, among the many factors that can impact sensitivity to the effects of drugs, this review emphasizes the importance of considering feeding conditions. Furthermore, elucidating the relationship between feeding conditions and drug response could facilitate our understanding of individual differences in response to therapeutic drugs and in vulnerability to drug abuse.

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Abbreviations

DA	dopamine
L-DOPA	L-dihydroxyphenylalanine
HVA	homovanillic acid
DOPAC	dihydroxyphenylacetic acid
DAT	dopamine transporter

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Figure 1.

Discriminative stimulus effects for cocaine, quinpirole, and lisuride in 6 free-feeding rats and in 6 food-restricted rats discriminating 10 mg/kg cocaine. Abscissa, feeding condition. Ordinate, maximum (mean $\pm$ SEM) percentage of responses on the cocaine lever. All 12 rats were trained to discriminate 10 mg/kg cocaine (i.p.) from vehicle (i.e. saline) under a schedule of stimulus shock termination. A cumulative-dosing, multiple-cycle procedure was used that included several 20-min cycles; each began with a 10-min timeout, during which stimulus lights were not illuminated and responding had no programmed consequence. The timeout period was followed by illumination of the house light signaling scheduled delivery of a brief electric stimulus every 10 s; a response on the injection-appropriate (correct) lever or the passage of 30 s turned off the house light, ended the trial, and initiated a 30-s timeout. If fewer than five trials were completed by a response on the correct lever in any cycle, the session ended. Test sessions were identical to training sessions except that a response on either lever postponed shock and either vehicle or increasing doses of drug were administered across cycles. Drugs were studied up to doses that occasioned greater than 80% responding on the cocaine lever or to the maximum doses that could be studied safely. The maximal dose shown for cocaine, quinpirole, and lisuride is 10, 1.0, and 1.0 mg/kg, respectively, for free-feeding rats and 10, 10, and 1.0 mg/kg, respectively, for food-restricted rats.

Table 1

The effects of food restriction on sensitivity to direct- and indirect-acting dopamine receptor agonists in rats

In Vivo Assay	Drug	Feeding Condition	Effect	Reference
Locomotor activity	Quinpirole (50 µg; i.c.v.)	10 g/day until 20% decrease in body weight	↑	Carr et al., 2003
Yawning	Quinpirole (0.01–1.0 mg/kg; i.p.)	10 g/day	↑ (Descending limb of dose-response curve)	Baladi and France, 2009
Hypothermia	Quinpirole (0.0032–0.32 mg/kg; i.p.)	Maintained ~320 g	x	Baladi et al., 2011
Locomotor activity	Pramipexole (0.01–1.0 mg/kg; s.c.)	85% of free-feeding body weight	↑	Collins et al., 2008
Yawning	Pramipexole (0.01–1.0 mg/kg; s.c.)	85% of free-feeding body weight	↑ (Descending limb of dose-response curve)	Collins et al., 2008
Hypothermia	Pramipexole (0.01–1.0 mg/kg; s.c.)	85% of free-feeding body weight	↑	Collins et al., 2008
Locomotor Activity	Amphetamine (1 mg/kg; i.p.)	80% of free-feeding body weight	↑	Deroche et al., 1993
Self-administration	Amphetamine (0.05, 0.2, 0.8 mg/kg/infusion)	80% of free-feeding body weight	↑	Takahashi et al., 1978
Locomotor Activity	Cocaine (15 mg/kg; i.p.)	90% of free-feeding body weight	↑	Stamp et al., 2008
Self-Administration	Cocaine (0.2 mg/kg/infusion)	8 g for 24 hours	↑	Carroll et al., 1981

Table 2

The effects of eating high fat chow on sensitivity to direct- and indirect-acting dopamine receptor agonists in rats

In Vivo Assay	Drug	Feeding Condition	Effect	Reference
Drug discrimination	Quinpirole (0.0032–0.032 mg/kg; i.p.)	34.3% fat (by weight); 5.1 kcal/g	↑	Baladi and France, 2010
Yawning	Quinpirole (0.0032–0.32 mg/kg; i.p.)	34.3% fat (by weight); 5.1 kcal/g	↑	Baladi and France, 2010
Conditioned-place preference	Amphetamine (1 mg/kg; i.p.)	24% fat (by weight); 4.7 kcal/g	↓	Davis et al., 2008
Locomotor Activity	Methamphetamine (0.1–10 mg/kg; i.p.)	34.3% fat (by weight); 5.1 kcal/g	↑	McGuire et al., 2011
Self-administration (acquisition)	Cocaine (0.2 mg/kg/infusion)	35.9% fat (by weight); 5.3 kcal/g	↓	Wellman et al., 2007