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Invited review

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 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.

This article is part of a Special Issue entitled 'Central Control of Food Intake'.

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

Abbreviations: DA, dopamine; L-DOPA, L-dihydroxyphenylalanine; HVA, homovanillic acid; DOPAC, dihydroxyphenylacetic acid; DAT, dopamine transporter.

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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 (Ehringer and Hornykiewicz, 1960), 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, 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; Szczypka et al., 2001). Studies addressing central nervous system regulation of food intake are reviewed elsewhere in this journal edition and are beyond the