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Dopamine/adenosine interactions involved in effort-related aspects of food motivation

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Abstract

Nucleus accumbens dopamine (DA) is involved in effort-related aspects of food motivation. Accumbens DA depletions reduce the tendency of rats to work for food, and alter effort-related choice, but leave other aspects of food motivation and appetite intact. DA and adenosine receptors interact to regulate effort-related processes. Adenosine A_{2A} antagonists can reverse the effects of DA D_2 antagonists on effort-related choice, and intra-accumbens injections of a adenosine A_{2A} agonist produce effects that are similar to those produced by accumbens DA depletion or antagonism. These studies have implications for understanding the neurochemical interactions that underlie activational aspects of motivation.

Keywords

Operant; Reinforcement; Motivation; Behavioral economics; Reward; Decision making; Activation

Dopaminergic involvement in activational aspects of food motivation

Food motivation is a complex process, comprising several interacting but dissociable components. For several decades, research and theory in motivation has emphasized that there are both directional and activational aspects of motivation (Salamone, 1988). Directional aspects refer to the observation of that behavior is directed towards or away from particular motivational stimuli. In addition, it also is evident that motivated behavior can be characterized by persistence, vigor and high levels of work output. These activational aspects of motivation are adaptive because they enable organisms to overcome obstacles or work-related response costs that separate them from significant stimuli such as food (Salamone & Correa, 2002; Salamone, Correa, Farrar, & Mingote, 2007). Animals can forage in the wild, covering large areas of space and investing considerable amounts of time, in order to gain access to food or other primary motivational stimuli. In the laboratory, animals can perform in mazes, climb barriers, or vigorously press levers, to receive food reinforcement.

One of the brain systems that has been most vigorously studied in relation to aspects of motivation is the mesolimbic dopamine (DA) system. Though it is most commonly linked to drug reinforcement, nucleus accumbens DA also has been implicated in features of food motivation. In fact, there is little doubt that nucleus accumbens DA is involved in some aspects of food motivation. The difficult question is—which aspects? Reports indicating that nucleus accumbens DA release can be increased during presentation of food or food-related stimuli do not identify the specific aspects of motivation or learning in which DA is participating.

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Although it is generally recognized that whole forebrain DA depletions can produce aphagia (i.e., lack of eating), this effect has been conclusively linked to depletions of DA in the lateral or ventrolateral caudate/putamen, but not the nucleus accumbens (Dunnett & Iversen, 1982; Salamone, Kurth, McCullough, Sokolowski, & Cousins, 1993). Accumbens DA depletions do not substantially impair appetite for food, or produce a general disruption of all aspects of primary food motivation (Koob, Riley, Smith, & Robbins, 1978; Kelley, Baldo, Pratt, and Will, 2005; Salamone et al., 1993). Accumbens DA depletions did not reduce food intake or feeding rate, nor did they impair food handling, although similar depletions of ventrolateral neostriatum affected these parameters (Salamone et al., 1993). Based upon their observations that injections of DA D_1 or D_2 family antagonists into either core or shell subregions of nucleus accumbens impaired locomotion and rearing, but did not suppress food intake, Baldo, Sadeghian, Basso, and Kelley (2002) emphasized that DA receptor blockade "did not abolish the primary motivation to eat" (p. 176).

Although nucleus accumbens DA has not been strongly implicated in food consumption or appetite, considerable evidence indicates that accumbens DA is involved in behavioral activation, and, more specifically, in effort-related aspects of food motivation. Nucleus accumbens DA depletions have been shown to reduce spontaneous and novelty-induced locomotor activity and rearing, as well as stimulant-induced activity (Correa, Carlson, Wisniecki, & Salamone, 2002; Cousins, Sokolowski, & Salamone, 1993; Koob et al., 1978). Activities such as excessive drinking, wheel-running or locomotor activity that are induced by scheduled presentation of food pellets were reduced by accumbens DA depletions (McCullough & Salamone, 1992; Robbins & Koob, 1980). In addition, the effects of accumbens DA depletions on food-reinforced behavior vary greatly depending upon the specific task requirements of the schedule of food reinforcement. If the primary effects of accumbens DA depletions were related to a reduction in appetite for food, then the fixed ratio 1 (FR1) schedule should be highly sensitive to DA depletion. In fact, this schedule is one of the tasks that is least sensitive to the effects of compromised DA transmission in nucleus accumbens (Aberman & Salamone, 1999; McCullough, Cousins, & Salamone, 1993; Salamone, Kurth, McCullough, & Sokolowski, 1995). If time intervals without reinforcement were the most significant factor yielding sensitivity to the effects of impaired accumbens DA transmission, then one would expect that variable interval schedules would be easily disrupted by the effects of accumbens DA depletions or antagonism. Yet, these schedules are among the least sensitive (Correa et al., 2002; Mingote, Weber, Ishiwari, Correa, & Salamone, 2005; Sokolowski & Salamone, 1998). Several years of research has demonstrated that a critical factor yielding sensitivity to the effects of accumbens DA depletions on food reinforced behavior is the size of the ratio requirement; as ratio requirements get higher, rats become more sensitive to the response suppressing effects of accumbens DA depletions (Aberman & Salamone, 1999; Correa et al., 2002; Ishiwari, Weber, Mingote, Correa, & Salamone, 2004; Mingote et al., 2005). This pattern of results suggests that accumbens DA depletions leave fundamental aspects of appetite or primary food motivation intact, but reduce the tendency of the animals to work for food reinforcement.

Accumbens DA and effort-related choice behavior

Nucleus accumbens DA also is involved in effort-related choice behavior. In a complex environment there may be several sources of food available, which can vary in terms of quantity or quality. Furthermore, there can be multiple paths for obtaining access to each food location, and each path can require different responses that vary in terms of time, work, and other parameters. In order to generate adaptive behavior, animals must select between these alternatives, making effort-related decisions and allocating resources based upon cost/benefit analyses. Several behavioral paradigms have been developed that assess effort-based choice behavior. An operant concurrent choice task has been used that offers rats a choice between

lever pressing to obtain a preferred food (high carbohydrate pellets), vs. approaching and consuming a less preferred food (lab chow) that is concurrently available. Under non-drug conditions, rats pressing on an FR5 schedule typically get most of their food by lever pressing, and eat only small amounts of chow. Pre-feeding to reduce food motivation was shown to suppress both lever pressing and chow intake (Salamone et al., 1991). In contrast, the DA antagonists cis-flupenthixol, haloperidol, raclopride, eticlopride, ecopipam, SCH 23390, and SKF83566 all decreased lever pressing for food but substantially increased intake of the concurrently available chow (Salamone et al., 1991, 2007; Salamone, Arizzi, Sandoval, Cervone, & Aberman, 2002; Sink, Vemuri, Olszewska, Makriyannis, & Salamone, 2008; Worden et al., 2009). The low dose of haloperidol (0.1 mg/kg) that produced this effect did not alter food intake or preference in free-feeding choice tests (Salamone et al., 1991). Appetite suppressants such as fenfluramine and cannabinoid CB1 antagonists showed a very different pattern of effects from DA antagonists (Salamone et al., 2002; Sink et al., 2008), and did not increase chow intake at doses that suppress lever pressing. Together with the findings reviewed above, these results demonstrate that interference with DA transmission does not simply reduce appetite for food.

Nucleus accumbens, and not neostriatum, is the DA terminal region s most closely associated with these effects. Ventrolateral striatal DA depletions produced severe motor impairments that decreased both types of behavior (Cousins et al., 1993). Decreases in lever pressing and increases in chow intake result from accumbens DA depletions, as well as from intra-accumbens injections of D_1 or D_2 antagonists (Cousins & Salamone, 1994; Cousins et al., 1993; Koch, Schmid, & Schnitzler, 2000; Nowend, Arizzi, Carlson, & Salamone, 2001; Salamone et al., 1991; Sokolowski & Salamone, 1998). The shift from lever pressing to chow intake on this task has been shown to occur in rats if injections of a D_1 or D_2 family antagonist are given into various core or shell subregions of the accumbens (Nowend et al., 2001; Salamone et al., 1991). Thus, although lever pressing is decreased by accumbens DA antagonism or depletions, the rats show a compensatory reallocation of behavior and select a new path to an alternative food source.

A T-maze procedure also was developed to assess the effects of accumbens DA depletions on effort-related choice (Salamone, Cousins, & Bucher, 1994). The two choice arms of the maze can have different reinforcement densities (e.g. 4 food pellets vs. 2 food pellets, or 4 vs. 0), and under some conditions a 44 cm barrier can be placed in the arm with the higher density of food reinforcement to vary task difficulty. When no barrier is present in the arm with the high reinforcement density, rats mostly choose that arm, and neither haloperidol nor accumbens DA depletion alters their response choice (Salamone et al., 1994). When the arm with the barrier contained 4 pellets, but the other arm contained no pellets, DA depleted rats were relatively slow, but still chose the high density arm, climbed the barrier, and consumed the pellets (Cousins, Atherton, Turner, & Salamone, 1996). Yet, accumbens DA depletions dramatically altered choice when the high density arm (4 pellets) had the barrier in place, and the arm without the barrier contained an alternative food source (2 pellets). In this case, DA depleted rats showed decreased choice for the high density arm that contained the barrier, and increased choice for the arm with less food that did not have a barrier (Cousins et al., 1996; Salamone et al., 1994). These studies, together with the results of the operant concurrent choice studies, indicate that accumbens DA depletions cause animals to reallocate their instrumental response selection based upon the response requirements of the task (Salamone & Correa, 2002; Salamone et al., 2007).

In summary, rats with accumbens DA depletion or antagonism remain directed towards approaching and consuming food. Nevertheless, they have a reduced tendency to work for food, and their choice behavior is altered such that they become biased towards obtaining food through responses that have lower work-related costs. Thus, rats with impaired accumbens DA

transmission switch from lever pressing for preferred food pellets to approaching and consuming the less preferred chow, and they switch from climbing the barrier to obtain the higher density of food reinforcement towards the other arm of the maze, which has less food that can be obtained with a lower degree of effort.

DA and adenosine interact in the Regulation of behavioral activation and effort

As discussed above, substantial evidence indicates that DA antagonists and accumbens DA depletions are altering behavioral activation, instrumental response output, response allocation, effort-related processes (Floresco, Tse, & Ghods-Sharifi, 2008; Phillips, Walton, & Jhou, 2007; Robbins & Everitt, 2007; Salamone & Correa, 2002; Salamone et al., 1991, 2007). Of course, DA does not participate in effort-related processes in isolation, and for that reason it is important to review how other brain areas and neurotransmitters interact with dopaminergic mechanisms. Several studies have shown that basolateral amygdala, anterior cingulate cortex, and ventral pallidum also are involved (Farrar et al., 2008; Floresco & Ghods-Sharifi, 2007; Hauber & Sommer, in press; Mingote et al., 2008; Walton, Kennerley, Bannerman, Phillips, & Rushworth, 2006). Much recent work also has focused upon interactions between DA and adenosine.

Non-selective adenosine antagonists, such as caffeine and other methylxanthines, act as minor stimulants (Ferré et al., 2008). Within the last few years, there has been a rapid expansion of research on adenosine receptor pharmacology and neurochemistry, with particular emphasis on the A_{2A} receptor subtype. Striatal areas, including caudate/putamen (neostriatum) and also nucleus accumbens, are very rich in adenosine A_{2A} receptors (Fink et al., 1992). There is a functional interaction between striatal DA D_2 and adenosine A_{2A} receptors (Ferré, 1997; Fink et al., 1992), which frequently has been studied in regard to neostriatal motor functions that are related to parkinsonism (Correa et al., 2004; Ferré et al., 2001; Hauber, Neuscheler, Nagel, & Muller, 2001; Morelli & Pinna, 2002; Salamone et al., 2008). Researchers also have characterized aspects of adenosine A_{2A} receptor function related to anxiety (Correa & Font, 2008), cognitive processes (Takahashi, Pamplona, & Prediger, 2008) and motivation (Mingote et al., 2008; Salamone et al., 2007). Indeed, several recent studies have focused upon the motivational significance of adenosine A_{2A} receptors, and the interactions between adenosine and DA receptors, in relation to aspects of behavioral activation and effort-related processes (Farrar et al., 2007; Font et al., 2008; Mingote et al., 2008; Mott et al., 2009; Worden et al., 2009).

Intra-accumbens injections of the adenosine A_{2A} agonist CGS 21680 produce effects that resemble those of accumbens DA depletions or antagonism. CGS 21680 reduced locomotor activity when injected directly into nucleus accumbens (Barraco, Martens, Parizon, & Normile, 1993). A more recent paper has demonstrated that local injection of CGS 21680 into the accumbens reduced responding on a variable interval 60 s schedule with a FR10 requirement attached, but did not impair performance on a conventional variable interval 60 s schedule (Mingote et al., 2008), an effect that had previously been demonstrated to occur with accumbens DA depletions (Mingote et al., 2005). In rats responding on the operant FR5/chow feeding concurrent choice procedure, injections of CGS 21680 into the accumbens decreased lever pressing and increased chow intake (Font et al., 2008), a pattern of effects similar to that produced by accumbens DA depletions and antagonism. Consistent with the observation that an adenosine A_{2A} agonist could produce actions similar to those resulting from DA depletion, it also has been reported that adenosine A_{2A} receptor antagonists can reverse the effects of DA D_2 antagonists on both the operant concurrent choice task (Farrar et al., 2007; Worden et al., 2009) and the T-maze choice procedure (Mott et al., 2009).

Several lines of evidence indicate that there is a very specific interaction between DA D_2 and adenosine A_{2A} receptor subtypes. Although the adenosine A_{2A} receptor antagonists MSX-3 and KW 6002 can attenuate the effects of D_2 antagonists such as haloperidol and eticlopride in rats responding on the operant concurrent choice procedure (Farrar et al., 2007; Salamone et al., 2009; Worden et al., 2009), MSX-3 was shown to be relatively ineffective at reducing the effects of the D_1 antagonist ecopipam (SCH 39166; Worden et al., 2009). Furthermore, although the non-selective adenosine antagonist caffeine was able to partially reverse the effects of haloperidol on the concurrent choice task, the adenosine A_1 receptor selective antagonist DPCPX was ineffective (Salamone et al., 2009). Similar results were obtained with rats responding on the T-maze choice procedure with the barrier being used to provide the effort-related challenge. Although MSX-3 could reverse the attenuation of barrier climbing induced by haloperidol, the A_1 antagonist DPCPX was shown to be ineffective (Mott et al., 2009).

This pattern of results indicates that there is a relatively selective interaction between DA D_2 and adenosine A_{2A} receptors, and it is possible that this is related to the pattern of cellular localization of adenosine A_1 and A_{2A} receptors in striatal areas, including the nucleus accumbens (Ferré, 1997). Adenosine A_{2A} receptors generally are co-localized on striatal and accumbens medium spiny neurons with DA D_2 receptors (i.e., enkephalin positive medium spiny neurons), and these receptors converge onto the same signal transduction pathways and show the capacity for forming heteromeric complexes (Ferré, 1997; Fink et al., 1992). Thus, it is reasonable to suggest that adenosine A_{2A} receptor antagonists are so effective in reversing the effort-related actions of D_2 antagonists because of direct interactions between DA D_2 and adenosine A_{2A} receptors located on the same neurons. In contrast, DA D_1 receptors are more likely to be co-localized with adenosine A_1 receptors (Ferré, 1997). This pattern of receptor localization could help to explain why it is more difficult for adenosine A_1 receptor antagonists to reverse the effects of D_2 receptor blockade.

Summary and conclusions

In summary, there is considerable evidence that low doses of DA antagonists, as well as accumbens DA depletions or antagonism, while leaving fundamental aspects of appetite or primary food motivation intact, nevertheless reduce the tendency of animals to work for food reinforcement. Furthermore, adenosine A_{2A} antagonists can attenuate the effort-related behavioral effects of DA D_2 antagonists. The findings described above support the hypothesis that DA and adenosine systems in the nucleus accumbens interact in the regulation of instrumental response output and effort-related choice behavior (Farrar et al., 2007; Font et al., 2008; Mingote et al., 2008; Mott et al., 2009; Salamone et al., 2007, 2009; Worden et al., 2009), and they also illustrate the specific nature of the interaction between adenosine A_{2A} and DA D_2 receptors. Characterization of the neurochemical mechanisms involved in regulating behavioral activation and effort-based choice behavior can shed light on these important facets of natural motivation for food, and also have implications for understanding pathologies related to behavioral activation and effort (Salamone et al., 2007), such as anergia, psychomotor slowing, and fatigue in depression and other disorders (Demyttenaere, De Fruyt, & Stahl, 2005; Salamone et al., 2007). In addition, it is possible that A_{2A} receptor antagonists could be beneficial for ameliorating the motivational effects of D_2 antagonists that are used clinically, and also for treating other energy-related disorders (Salamone et al., 2007).

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References

Aberman JE, Salamone JD. Nucleus accumbens dopamine depletions make rats more sensitive to high ratio requirements but do not impair primary food reinforcement. Neuroscience 1999;92:545–552. [PubMed: 10408603]

Baldo BA, Sadeghian K, Basso AM, Kelley AE. Effects of selective dopamine D1 or D2 receptor blockade within nucleus accumbens subregions on ingestive behavior and associated motor activity. Behavioural Brain Research 2002;137:165–177. [PubMed: 12445722]

Barraco RA, Martens KA, Parizon M, Normile HJ. Adenosine A2a receptors in the nucleus accumbens mediate locomotor depression. Brain Research Bulletin 1993;31:397–404. [PubMed: 8490738]

Correa M, Font L. Is there a major role for adenosine A2A receptors in anxiety? Frontiers in Bioscience 2008;13:4058–4070. [PubMed: 18508500]

Correa M, Carlson BB, Wisniecki A, Salamone JD. Nucleus accumbens dopamine and work requirements on interval schedules. Behavioural Brain Research 2002;137:179–187. [PubMed: 12445723]

Correa M, Wisniecki A, Betz A, Dobson DR, O'Neill MF, O'Neill MJ, et al. The adenosine A2A antagonist KF17837 reverses the locomotor suppression and tremulous jaw movements induced by haloperidol in rats: possible relevance to parkinsonism. Behavioural Brain Research 2004;148:47–54. [PubMed: 14684247]

Cousins MS, Salamone JD. Nucleus accumbens dopamine depletions in rats affect relative response allocation in a novel cost/benefit procedure. Pharmacology Biochemistry and Behavior 1994;49:85–91.

Cousins MS, Sokolowski JD, Salamone JD. Different effects of nucleus accumbens and ventrolateral striatal dopamine depletions on instrumental response selection in the rat. Pharmacology Biochemistry and Behavior 1993;46:951–953.

Cousins MS, Atherton A, Turner L, Salamone JD. Nucleus accumbens dopamine depletions alter relative response allocation in a T-maze cost/benefit task. Behavioural Brain Research 1996;74:189–197. [PubMed: 8851929]

Demyttenaere K, De Fruyt J, Stahl SM. The many faces of fatigue in major depressive disorder. International Journal of Neuropsychopharmacology 2005;8:93–105. [PubMed: 15482632]

Dunnett SB, Iversen SD. Regulatory impairments following selective 6-OHDA lesions of the neostriatum. Behavioural Brain Research 1982;4:195–202. [PubMed: 7059376]

Farrar AM, Pereira M, Velasco F, Hockemeyer J, Muller CE, Salamone JD. Adenosine A(2A) receptor antagonism reverses the effects of dopamine receptor antagonism on instrumental output and effort-related choice in the rat: implications for studies of psychomotor slowing. Psychopharmacology 2007;191:579–586. [PubMed: 17072593]

Farrar AM, Font L, Pereira M, Mingote SM, Bunce JG, Chrobak JJ, et al. Forebrain circuitry involved in effort-related choice: injections of the $GABA_A$ agonist muscimol into ventral pallidum alters response allocation in food-seeking behavior. Neuroscience 2008;152:321–330. [PubMed: 18272291]

Ferré S. Adenosine-dopamine interactions in the ventral striatum. Implications for the treatment of schizophrenia. Psychopharmacology 1997;133:107–120. [PubMed: 9342776]

Ferré S, Popoli P, Giménez-Llort L, Rimondini R, Müller CE, Strömberg I, et al. Adenosine/dopamine interaction: implications for the treatment of Parkinson's disease. Parkinsonism and Related Disoders 2001;7:235–241.

Ferré S, Ciruela F, Borycz J, Solinas M, Quarta D, Antoniou K, et al. Adenosine A1-A2A receptor heteromers: new targets for caffeine in the brain. Frontiers in Bioscience 2008;13:2391–2399. [PubMed: 17981720]

Fink JS, Weaver DR, Rivkees SA, Peterfreund RA, Pollack AE, Adler EM, et al. Molecular cloning of the rat A_{2A} adenosine receptor: selective co-expression with D_2 dopamine receptors in rat striatum. Brain Research Molecular Brain Research 1992;14:186–195. [PubMed: 1279342]

Floresco SB, Ghods-Sharifi S. Amygdala-prefrontal cortical circuitry regulates effort-based decision making. Cerebral Cortex 2007;17:251–260. [PubMed: 16495432]

Floresco SB, Tse MT, Ghods-Sharifi S. Dopaminergic and glutamatergic regulation of effort- and delay-based decision making. Neuropsychopharmacology 2008;33:1966–1979. [PubMed: 17805307]

Font L, Mingote S, Farrar AM, Pereira M, Worden L, Stopper C, et al. Intra-accumbens injections of the adenosine A(2A) agonist CGS 21680 affect effort-related choice behavior in rats. Psychopharmacology 2008;199:515–526. [PubMed: 18491078]

Hauber W, Sommer S. Prefrontostriatal circuitry regulates effort-related decision making. Cerebral Cortex. in press.

Hauber W, Neuscheler P, Nagel J, Muller CE. Catalepsy induced by a blockade of dopamine D_1 or D_2 receptors was reversed by a concomitant blockade of adenosine A_{2A} receptors in the caudate putamen of rats. European Journal of Neuroscience 2001;14:1287–1293. [PubMed: 11703457]

Ishiwari K, Weber SM, Mingote S, Correa M, Salamone JD. Accumbens dopamine and the regulation of effort in food-seeking behavior: modulation of work output by different ratio or force requirements. Behavioural Brain Research 2004;151:83–91. [PubMed: 15084424]

Kelley AE, Baldo BA, Pratt WE, Will MJ. Corticostriatal-hypothalamic circuitry and food motivation: integration of energy, action and reward. Physiological Behavior 2005;86:773–795.

Koch M, Schmid A, Schnitzler HU. Role of nucleus accumbens dopamine D_1 and D_2 receptors in instrumental and Pavlovian paradigms of conditioned reward. Psychopharmacology 2000;152:67–73. [PubMed: 11041317]

Koob GF, Riley SJ, Smith SC, Robbins TW. Effects of 6-hydroxydopamine lesions of the nucleus accumbens septi and olfactory tubercle on feeding, locomotor activity, and amphetamine anorexia in the rat. Journal of Comparative and Physiological Psychology 1978;92:917–927. [PubMed: 282297]

McCullough LD, Salamone JD. Involvement of nucleus accumbens dopamine in the motor activity induced by periodic food presentation: a microdialysis and behavioral study. Brain Research 1992;592:29–36. [PubMed: 1450917]

McCullough LD, Cousins MS, Salamone JD. The role of nucleus accumbens dopamine in responding on a continuous reinforcement operant schedule: a neurochemical and behavioral study. Pharmacology Biochemistry and Behavior 1993;46:581–586.

Mingote S, Weber SM, Ishiwari K, Correa M, Salamone JD. Ratio and time requirements on operant schedules: effort-related effects of nucleus accumbens dopamine depletions. European Journal of Neuroscience 2005;21:1749–1757. [PubMed: 15845103]

Mingote S, Font L, Farrar AM, Vontell R, Worden LT, Stopper CM, et al. Nucleus accumbens adenosine A2A receptors regulate exertion of effort by acting on the ventral striatopallidal pathway. Journal of Neuroscience 2008;28:9037–9046. [PubMed: 18768698]

Morelli M, Pinna A. Interaction between dopamine and adenosine A_{2A} receptors as a basis for the treatment of Parkinson's disease. Neurological Sciences 2002;22:71–72. [PubMed: 11487207]

Mott AM, Nunes EJ, Collins LE, Port RG, Sink KS, Hockemeyer J, et al. The adenosine A_{2A} antagonist MSX-3 reverses the effects of the dopamine antagonist haloperidol on effort-related decision making in a T-maze cost/benefit procedure. Psychopharmacology 2009;204:103–112. [PubMed: 19132351]

Nowend KL, Arizzi M, Carlson BB, Salamone JD. D_1 or D_2 antagonism in nucleus accumbens core or dorsomedial shell suppresses lever pressing for food but leads to compensatory increases in chow consumption. Pharmacology Biochemistry and Behavior 2001;69:373–382.

Phillips PE, Walton ME, Jhou TC. Calculating utility: preclinical evidence for cost–benefit analysis by mesolimbic dopamine. Psychopharmacology 2007;191:483–495. [PubMed: 17119929]

Robbins TW, Everitt BJ. A role for mesencephalic dopamine in activation: commentary on Berridge (2006). Psychopharmacology 2007;191:433–437. [PubMed: 16977476]

Robbins TW, Koob GF. Selective disruption of displacement behaviour by lesions of the mesolimbic dopamine system. Nature 1980;285:409–412. [PubMed: 6104303]

Salamone JD. Dopaminergic involvement in activational aspects of motivation: effects of haloperidol on schedule induced activity, feeding and foraging in rats. Psychobiology 1988;16:196–206.

Salamone JD, Correa M. Motivational views of reinforcement: implications for understanding the behavioral functions of nucleus accumbens dopamine. Behavioural Brain Research 2002;137:3–25. [PubMed: 12445713]

Salamone JD, Steinpreis RE, McCullough LD, Smith P, Grebel D, Mahan K. Haloperidol and nucleus accumbens dopamine depletion suppress lever pressing for food but increase free food consumption in a novel food choice procedure. Psychopharmacology 1991;104:515–521. [PubMed: 1780422]

Salamone JD, Kurth PA, McCullough LD, Sokolowski JD, Cousins MS. The role of brain dopamine in response initiation: effects of haloperidol and regionally specific dopamine depletions on the local rate of instrumental responding. Brain Research 1993;628:218–226. [PubMed: 8313150]

Salamone JD, Cousins MS, Bucher S. Anhedonia or anergia? Effects of haloperidol and nucleus accumbens dopamine depletion on instrumental response selection in a T-maze cost/benefit procedure. Behavioural Brain Research 1994;65:221–229. [PubMed: 7718155]

Salamone JD, Kurth P, McCullough LD, Sokolowski JD. The effects of nucleus accumbens dopamine depletions on continuously reinforced operant responding: contrasts with the effects of extinction. Pharmacology Biochemistry and Behavior 1995;50:437–443.

Salamone JD, Arizzi M, Sandoval MD, Cervone KM, Aberman JE. Dopamine antagonsts alter response allocation but do not suppress appetite for food in rats: contrast between the effects of SKF 83566, raclopride and fenfluramine on a concurrent choice task. Psychopharmacology 2002;160:371–380. [PubMed: 11919664]

Salamone JD, Correa M, Farrar A, Mingote SM. Effort-related functions of nucleus accumbens dopamine and associated forebrain circuits. Psychopharmacology 2007;191:461–482. [PubMed: 17225164]

Salamone JD, Ishiwari K, Betz AJ, Farrar AM, Mingote SM, Font L, et al. Dopamine/adenosine interactions related to locomotion and tremor in animal models: possible relevance to parkinsonism. Parkinsonism and Related Disorders 2008;14:S130–S134. [PubMed: 18585081]

Salamone JD, Farrar AM, Font L, Patel V, Schlar DE, Nunes EJ, et al. Differential actions of adenosine A1 and A2A antagonists on the effort-related effects of dopamine D2 antagonism. Behavioural Brain Research 2009;201:216–222. [PubMed: 19428636]

Sink KS, Vemuri VK, Olszewska T, Makriyannis A, Salamone JD. Cannabinoid CB1 antagonists and dopamine antagonists produce different effects on a task involving response allocation and effort-related choice in food-seeking behavior. Psychopharmacology 2008;196:565–574. [PubMed: 18004546]

Sokolowski JD, Salamone JD. The role of nucleus accumbens dopamine in lever pressing and response allocation: effects of 6-OHDA injected into core and dorsomedial shell. Pharmacology Biochemistry and Behavior 1998;59:557–566.

Takahashi RN, Pamplona FA, Prediger RD. Adenosine receptor antagonists for cognitive dysfunction: a review of animal studies. Frontiers in Bioscience 2008;13:2614–2632. [PubMed: 17981738]

Walton ME, Kennerley SW, Bannerman DM, Phillips PE, Rushworth MF. Weighing up the benefits of work: behavioral and neural analyses of effort-related decision making. Neural Network 2006;19:1302–1314.

Worden LT, Shahriari M, Farrar AM, Sink KS, Hockemeyer J, Müller C, et al. The adenosine A_{2A} antagonist MSX-3 reverses the effort-related effects of dopamine blockade: differential interaction with D1 and D2 family antagonists. Psychopharmacology 2009;203:489–499. [PubMed: 19048234]