Review
Future Neurology

Role of dopamine–adenosine interactions in the brain circuitry regulating effort-related decision making: insights into pathological aspects of motivation

John D Salamone[†1], Merce Correa[1,2], Andrew M Farrar[3], Eric J Nunes[1] & Lyndsey E Collins[1]

[1]Division of Behavioral Neuroscience, Department of Psychology, University of Connecticut, Storrs, CT 06269-1020, USA
[2]Department Psicologia, Universitat Jaume I, Castello, Spain
[3]Center for Molecular & Behavioral Neuroscience, Rutgers University, NJ, USA
[†]Author for correspondence: Tel.: +1 860 486 4302 ■ Fax: +1 860 486 2760 ■ john.salamone@uconn.edu

Brain dopamine, particularly in the nucleus accumbens, has been implicated in activational aspects of motivation and effort-related processes. Accumbens dopamine depletions reduce the tendency of rats to work for food, and alter effort-related decision making, but leave aspects of food motivation such as appetite intact. Recent evidence indicates that the purine neuromodulator adenosine, largely through actions on adenosine A_{2A} receptors, also participates in regulating effort-related processes. Adenosine A_{2A} antagonists can reverse the effects of dopamine D_2 antagonists on effort-related choice, and intra-accumbens injections of adenosine A_{2A} agonists produce effects that are similar to those induced by accumbens dopamine depletion or antagonism. These studies have implications for the understanding and treatment of energy-related disorders such as anergia and fatigue in psychiatry and neurology.

Dopaminergic involvement in activational aspects of motivation

Similar to other psychological constructs such as emotion and cognition, motivation is not a simple or unitary phenomenon. Motivation is a complex and multifacted process that includes many diverse components. Some aspects of motivation are related to sensations of internal and external stimuli, while other aspects of motivation are related to motor function [1]. Motivated behavior takes place in phases that represent different degrees of physical or psychological distance from the primary motivational stimulus (i.e., appetitive vs consummatory; instrumental vs consummatory; see [2–4]). Moreover, motivation theory and research has emphasized for several years that there are 'directional' and 'activational' aspects of motivation [5–7]. Directional aspects refer to the observation that the behavior of animals is directed towards or away from particular motivational stimuli. In addition, it is evident that motivated behavior can be characterized by persistence, vigor and high levels of work output; these activational aspects of motivated behavior are highly adaptive because they enable organisms to overcome challenges or work-related response costs that separate them from significant stimuli such as food [4,8–13]. While foraging in the wild, animals can invest considerable time and can cover large areas of space in order to gain access to food or other primary motivational stimuli. Laboratory experiments have shown that animals can climb barriers, run in mazes or press levers on schedules with high input ratio requirements, in order to gain access to motivational stimuli such as food. Under some conditions the presentation of motivational stimuli can generate heightened, even excessive, levels of motor activity. In humans, impairments in behavioral activation can manifest themselves as energy-related symptoms such as psychomotor slowing, anergia and fatigue, which are features of depression, and can also be observed in other psychiatric or neurological disorders [11].

In addition to studying these behavioral processes involved in activational aspects of motivation, neuroscientists have also focused upon the brain mechanisms that are potentially involved. Several brain areas have been investigated, but one of the neural systems most closely associated with behavioral activation is the dopamine (DA) innervation of the nucleus accumbens [8–11,14,15]. Although the mesolimbic DA system has consistently been linked to aspects of drug reinforcement, and is often referred to as some type of 'pleasure' or 'reward' center, recent

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research has demonstrated that the story is much more complicated and there are signs of a 'paradigm shift' taking place in this field [11,16]. In fact, neither DA antagonists, whole forebrain DA depletions or localized DA depletions in nucleus accumbens affect appetitive taste reactivity for food [17–20]; these findings have consistently been interpreted to suggest that interference with mesolimbic DA transmission does not blunt the hedonic reaction to food (i.e., 'liking'). Although Gunne and colleagues reported that the hedonic effects of amphetamine could be blocked by DA D_2 receptor antagonism [21], considerable research has failed to support this hypothesis [22–24]. The D_1 antagonist ecopipam did not blunt either the self-administration or the subjective pleasure induced by cocaine [25,26]. In addition, catecholamine depletion induced by feeding individuals a phenylalanine/tyrosine-free diet did not reduce cocaine-induced hedonia or self-administration [27]. In this context, it is worth noting that substantial literature has linked nucleus accumbens in general, and its DA innervation in particular, to aspects of aversive learning, aversive motivation and stress [28–44]. It is generally recognized that whole forebrain DA depletions can produce aphagia (i.e., lack of eating); however, in animals, this effect has been conclusively linked to motor or sensorimotor impairments induced by depletions of DA in the lateral or ventrolateral caudate/putamen, but not to actions upon the nucleus accumbens [44–47]. Several papers have shown that nucleus accumbens DA depletions do not substantially impair appetite for food, or produce a broad disruption of directional aspects of primary food motivation [46–48]. Depletions of DA in nucleus accumbens failed to reduce food intake or feeding rate, and did not impair food handling, although similar depletions in the ventrolateral neostriatum did affect these measures of feeding [46]. DA D_1 or D_2 family antagonists injected into either the core or the shell subregions of nucleus accumbens impaired locomotion and rearing, but did not suppress food intake, which led Baldo *et al.* to conclude that DA receptor antagonism "did not abolish the primary motivation to eat" [49]. Several studies have demonstrated that nucleus accumbens DA depletions, as well as systemic or intra-accumbens DA antagonism, do not produce effects that closely resemble those resulting from motivational manipulations, such as prefeeding or appetite suppressant drugs [50–54]. Thus, despite claims to the contrary, nucleus accumbens DA has not been strongly implicated in food consumption, appetite or primary food motivation [13]. Similar arguments have been made with regard to other motivational conditions, including sexual and maternal behaviors [55–58].

By contrast, an enormous body of evidence demonstrates that nucleus accumbens DA is involved generally in behavioral activation and, more specifically, in effort-related aspects of food motivation. Accumbens DA depletions reduced spontaneous and novelty-induced locomotor activity and rearing, as well as stimulant-induced activity [48,59,60]. Behaviors such as excessive drinking, wheel-running or locomotor activity, which are induced by scheduled presentation of food pellets to food-deprived animals, were reduced by accumbens DA depletions [61–63]. Furthermore, the effects of nucleus accumbens DA depletions on food-reinforced instrumental behavior depend greatly upon the specific task requirements of the schedule of food reinforcement. Schedules with minimal work requirements, such as a fixed ratio (FR) 1, and variable interval (VI) or progressive interval schedules, are relatively insensitive to the effects of accumbens DA depletions [59,64–72]. In fact, one of the critical factors that makes a food-reinforced operant task sensitive to the effects of accumbens DA depletions is the size of the ratio requirement (i.e., the number of times they have to press the lever to receive food); as ratio requirements get higher, rats become more sensitive to the response-suppressing effects of accumbens DA depletions [66–68,70–72]. The impact of ratio requirement as a factor that leads to increased sensitivity to the effects of accumbens DA depletions is not simply dependent upon the degree of intermittence in the schedule (i.e., the time spent with no primary reinforcers). While performance on VI 30, 60 or 120 s schedules was minimally affected by accumbens DA depletions, attachment of a ratio requirement (FR5 or 10) to the interval requirement made these schedules highly sensitive to the response-suppressing effects of accumbens DA depletions [59,68]. Together with studies of food intake, this pattern of results indicates that nucleus 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 dopamine & effort-related decision making

In a complex environment there may be several motivational stimuli available concurrently (e.g., different types of food), which can vary in terms

of quantity or quality. Typically, there would also be diverse patterns of instrumental behavior that are necessary for obtaining access to each stimulus, with response requirements that vary in terms of time, work and other parameters. Thus, in order to adapt to these conditions, organisms must select between various alternatives, making effort-related decisions and allocating behavioral resources based upon numerous factors related to response cost and reinforcement value. In addition to being involved in the exertion of effort, nucleus accumbens DA also participates in the process of effort-related choice behavior.

A number of behavioral procedures have been developed that allow for the assessment of how animals allocate resources based upon analyses of reinforcement value and response cost. For example, a T-maze procedure was developed to assess the effects of accumbens DA depletions on response choice based upon task difficulty [73]. The two choice arms of the maze can have different reinforcement densities (e.g., four vs two food pellets, or four vs zero), and in order to provide an effort-related challenge, a 44-cm barrier can be placed in the arm with the higher density of food reinforcement (Figure 1). When no barrier is present in the arm with the high reinforcement density, rats strongly prefer that arm, and neither haloperidol nor accumbens DA depletion alters their response choice [73]. When the arm with the barrier contained four food pellets, but the other arm contained no pellets, so that the only way to obtain food was by climbing the barrier, rats with accumbens DA depletions still chose the high-density arm, climbed the barrier and consumed the pellets [74]. These control experiments indicated that interference with DA transmission did not impair memory for which arm had the most pellets, did not affect the discrimination of reinforcement density and did not alter arm preference. Nevertheless, low doses of DA antagonists and accumbens DA depletions dramatically altered choice behavior when the high-density arm (four pellets) had the barrier in place, and the arm without the barrier contained an alternative food source (two pellets). Under these conditions, rats with impaired DA transmission 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 [73–75]. More recently, a mouse version of the T-maze task has been developed [76]. As with rats, the DA antagonist haloperidol decreased selection of the arm with the barrier in mice, but increased selection of the arm with no barrier, which contained a lower density of food reward. Interestingly, the same doses of haloperidol had no effect on choice when both arms were blocked by barriers; this observation confirms that the haloperidol-treated mice were capable of climbing the barrier, and remembered which arm had the higher density of reward, but these mice chose not to climb the barrier when there was an alternative food source available that could be reached with less effort. Taken together, these experiments indicate that accumbens DA depletions cause animals to reallocate their instrumental responses based upon the response requirements of the task (reviewed in [8–11,77]).

Another task that has been developed is an operant concurrent choice procedure that offers rats a choice between lever pressing to obtain a preferred food (high carbohydrate pellets), versus approaching and consuming a less preferred food (laboratory chow) that is concurrently available. Under baseline or control conditions, rats responding on FR1 or FR5 schedules typically get most of their food by lever pressing, and they eat minimal quantities of chow. However, low-to-moderate doses of DA antagonists with varying degrees of selectivity produce a substantial alteration of response allocation. The DA antagonists *cis*-flupenthixol, haloperidol, raclopride, eticlopride, SCH 23390, SKF83566 and ecopipam (SCH 39166) all decreased lever pressing for food but substantially increased intake of the concurrently available chow [51,53,54,77,78]. By contrast, knockdown of the DA transporter in mice resulted in the opposite effect; that is, increases in lever pressing and decreases in chow intake [79]. The nucleus accumbens, rather than the neostriatum, is the DA terminal region most closely associated with the effects of DA depletion or antagonism. Ventrolateral neostriatal DA depletions produced severe motor impairments that merely decreased both types of behavior, while injections of 6-hydroxydopamine into the anteroventromedial neostriatum were ineffective [80]. Decreases in lever pressing and increases in chow intake were produced by accumbens DA depletions, as well as by intra-accumbens injections of D_1 or D_2 family antagonists [51,66,80–84]. The shift from lever pressing to chow intake on this task has been demonstrated to occur if injections of D_1 or D_2 family antagonists were administered into the medial core, lateral core or dorsomedial shell subregions of the accumbens [51,82–84]. Although injections of the D_2 antagonist, eticlopride, into nucleus accumbens core shifted behavior from lever pressing to chow intake, injections into a dorsomedial neostriatal control site were ineffective [84]. Thus, despite the fact that lever pressing is decreased by accumbens

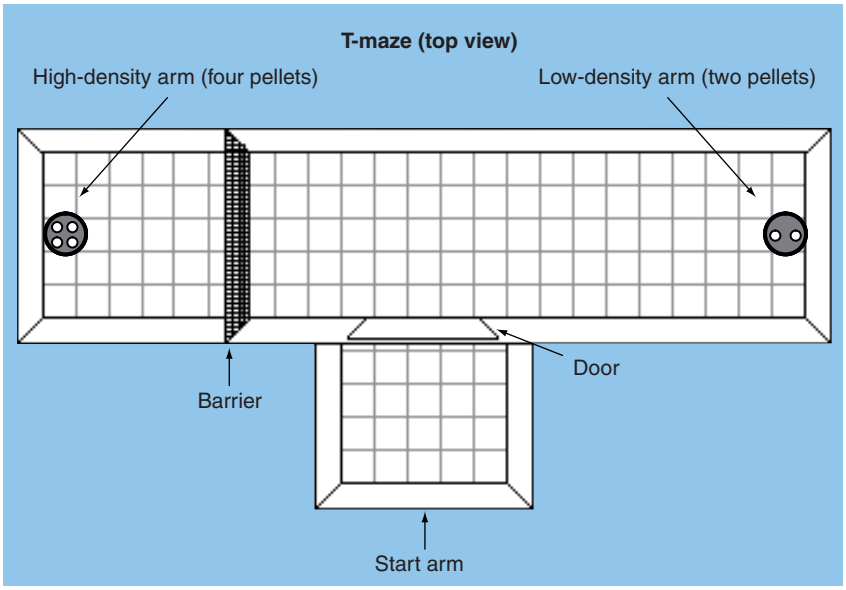

Figure 1. Top view of the T-maze apparatus used in the Mott *et al.* 2009 study. The start arm of the maze consisted of an enclosed plexiglas box (29 × 21 × 21 cm) with a wire mesh floor grid. The test arm of each side of the maze was a box 99 × 32 × 59 cm. The test arm and back walls of the maze were constructed out of Plexiglas®, and the floor was wire mesh. The doorway from the start arm to the maze was a stainless steel guillotine door. The barrier (depicted in the high-density arm, to the left) was constructed of wire mesh (44 × 32 cm). The high-density arm contained four food pellets, and the low-density arm contained two food pellets.
Taken from [75].

DA antagonism or depletions, the rats show a compensatory reallocation of behavior and select a new path to an alternative food source.

Several control experiments have been conducted in order to characterize the significance of these effects with dopaminergic manipulations. For example, behavioral experiments demonstrated that the concurrent choice task is sensitive to both the type of food being offered [85] and the work requirement of the lever pressing task [8]. Other studies have indicated that interference with accumbens DA transmission does not appear to produce a severe impairment in motor capacity. Injections of DA D_1 or D_2 family antagonists into the nucleus accumbens core and shell that produced the shift from lever pressing to chow intake did not increase lever press response duration [83], which indicates that these manipulations were not producing catalepsy (for a discussion of response duration, see [86]). These observations are consistent with a report showing that rats with mild accumbens DA depletions could still demonstrate the shift from FR5 lever pressing to chow intake even when separate tests demonstrated that there was no significant impairment in responding when the FR5 schedule was available without food being present [81]. Parallel studies with free-feeding choice tests indicated that preference for the pellets over the laboratory chow, as well as food intake, were not affected by the various conditions that produce the shift from lever pressing to chow intake; this includes administration of low doses of haloperidol [51], as well as intra-accumbens injections of sulpiride or SCH 23390 [82]. With rats performing on the concurrent choice task, prefeeding to reduce food motivation was demonstrated to suppress both lever pressing and chow intake [51]. Although DA antagonists have been shown to reduce FR 5 lever pressing and increase chow intake, appetite suppressants such as fenfluramine and cannabinoid CB1 antagonists showed a very different pattern of effects [53,54], and did not increase chow intake at doses that suppress lever pressing. Together with the other results (reviewed previously), these findings demonstrate that interference with DA transmission does not simply reduce appetite for food.

In summary, animals administered low doses of DA antagonists, or those with accumbens DA depletions, remain directed towards the acquisition and consumption of food. Furthermore, they do not show severe impairments in motor capacity. Nevertheless, they manifest 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 alternative arm of the maze, which has less food that can be obtained with a lower degree of effort. The results of these studies are consistent with recent papers demonstrating that DA antagonists also affect effort discounting [87,88]. Bardgett *et al.* developed an effort-discounting version of the T-maze task [88], in which the amount of food in the high-density arm of the maze was diminished every time the rats selected that arm. Their results demonstrated that both the D_1 family antagonist SCH23390 and the D_2 family antagonist haloperidol altered effort discounting, making it more likely that rats would choose the arm with the smaller reward. Moreover, they observed that amphetamine produced the opposite effect, making it easier for rats to tolerate greater exertion of effort. Floresco *et al.* reported that haloperidol affected effort discounting even when one controlled for any

possible time delays caused by completing the ratio [87]. Taken together, these results indicate that DA systems participate in the regulation of effort-based decision making.

Forebrain circuits & neurotransmitter interactions regulating effort-related processes

Although interference with accumbens DA transmission can exert profound effects on some aspects of motivation, these effects do not appear to be a result of actions such as appetite suppression or reductions in the primary or unconditioned motivation for food [8,11,15,49,77,89]. Instead, considerable evidence indicates that DA antagonists and accumbens DA depletions alter functions such as behavioral activation, instrumental response output and allocation, and effort-related processes [8,11,14,15,49,77,87–92]. Of course, accumbens DA does not regulate effort-related processes in isolation, and for that reason it is important to review how other brain areas and neurotransmitters are involved. Several recent studies have shown that anterior cingulate cortex, basolateral amygdala and ventral pallidum also participate in effort-related processes [93–97]. The T-maze task previously described [73] has been employed to investigate the functions of frontal/cingulate cortical areas in addition to the accumbens. Walton *et al.* studied the effects of medial frontal cortex lesions that included prelimbic, infralimbic and anterior cingulate cortex, and demonstrated that these lesions shifted the behavior of the rats away from the arm that contained the high density of reinforcement that was obstructed by a barrier [94]. In a subsequent paper, lesions of the prelimbic and infralimbic cortex did not affect choice behavior, but lesions of the anterior cingulate cortex produced the same changes in effort-related choice that had been shown previously with the larger lesions [95]. Large anterior cingulate catecholamine depletions were shown to affect T-maze choice behavior [96]. Furthermore, bilateral inactivation of anterior cingulate cortex also shifted choice behavior in the T-maze [97].

Recent research in this area has also focused on interactions between DA and the purine neuromodulator, adenosine. Four G-protein-coupled adenosine receptors have been identified, although the A_1 and A_{2A} subtypes predominate in the brain [98]. It has been known for some time that nonselective adenosine antagonists, such as caffeine and theophylline, act as minor stimulants [99]. Over the last two decades, there has been a tremendous growth in research on adenosine receptor neurochemistry and pharmacology, and the A_{2A} receptor subtype has received considerable attention. Both caudate/putamen (neostriatum) and nucleus accumbens are very rich in adenosine A_{2A} receptors [100–103]. There is a neurochemical interaction between striatal DA D_2 and adenosine A_{2A} receptors, which tend to be colocalized on the same enkephalin-positive medium spiny neurons [102–108]. The behavioral significance of this interaction has frequently been studied in the context of neostriatal motor functions and dysfunctions that are related to parkinsonism [104,105,109–116]. Investigators have also studied adenosine A_{2A} receptor pharmacology in relation to cognitive processes [117] and anxiety [118]. Within the last few years, the motivational significance of adenosine A_{2A} receptor pharmacology has become apparent, especially with regard to aspects of behavioral activation and effort-related processes [84,119–121].

Broadly speaking, injections of the adenosine A_{2A} agonist, CGS 21680, directly into nucleus accumbens have been shown to produce effects that resemble those of accumbens DA depletions or antagonism. Intra-accumbens injections of CGS 21680 reduced locomotor activity [122]. More recently, it was demonstrated that local injection of CGS 21680 into nucleus accumbens core reduced response on a VI 60 s schedule with an attached FR10 requirement attached, but did not impair performance on a standard VI 60 s schedule [121], an effect that has been shown to occur following accumbens DA depletions [68]. In rats responding to the operant FR5/chow feeding concurrent choice procedure, injections of CGS 21680 into the accumbens core decreased lever pressing and increased chow intake [120], a pattern of effects similar to that produced by accumbens DA depletions and antagonism. Injections of CGS 21680 into a control site dorsal to nucleus accumbens were ineffective [120].

Consistent with the observation that an adenosine A_{2A} agonist could produce actions similar to those resulting from interference with DA transmission, it has also been demonstrated that adenosine A_{2A} receptor antagonists can reverse the effects of DA antagonists on effort-related choice behavior. Studies employing the T-maze barrier choice procedure demonstrated that the adenosine A_{2A} receptor antagonist, MSX-3, could reverse the effects of the D_2 antagonist haloperidol in both rats [75] and mice [76]. MSX-3 also reversed the effects of the D_2 antagonists haloperidol and eticlopride in rats responding on the concurrent lever pressing/chow feeding procedure [79,84,119].

Similar effects have been produced by another adenosine A_{2A} receptor antagonist, istradefylline (KW 6002; [78, Nunes EJ, Randall PA, Santerre JL *et al.*, Unpublished Data]). These pharmacological studies indicate that there is a very specific interaction between DA D_2 and adenosine A_{2A} receptor subtypes. Although the adenosine A_{2A} receptor antagonist MSX-3 can reduce the effect of haloperidol in rats and mice responding on the T-maze task, the A_1 antagonists, 8-cyclopentyl-1,3-dipropylxanthine (DPCPX) and 8-cyclopentyltheophylline (CPT) were ineffective [75,76]. Similarly, DPCPX and CPT were unable to reverse the effects of haloperidol and eticlopride in rats responding on the operant concurrent choice task [78, Nunes EJ, Randall PA, Santerre JL *et al.*, Unpublished Data]. Despite the fact that both MSX-3 and istradefylline could reverse the effects of D_2 antagonists, such as haloperidol and eticlopride, in rats responding on the operant concurrent choice procedure [78,119,123], these drugs produced only a mild attenuation the effects of the D_1 antagonists ecopipam (SCH 39166) and SCH 23390 [123, Nunes EJ, Randall PA, Santerre JL *et al.*, Unpublished Data]. Furthermore, the adenosine A_1 antagonists DPCPX and CPT were unable to reverse the effects of the DA D_1 antagonist ecopipam [Nunes EJ, Randall PA, Santerre JL *et al.*, Unpublished Data]. Similar results were obtained with rats tested on a novelty-induced locomotion procedure [124].

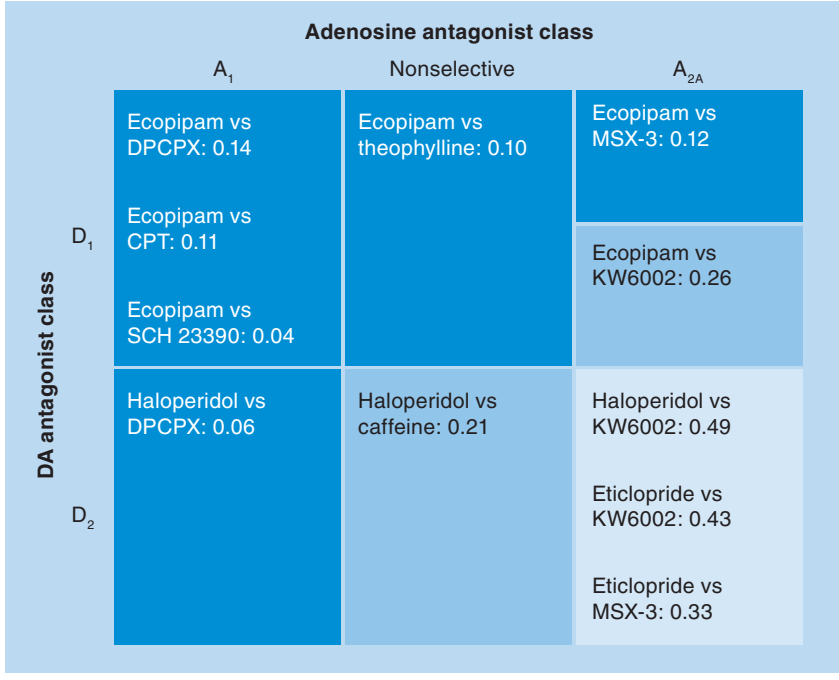

Figure 2. Summary of drug reversal studies with the operant concurrent choice task. This chart lists the effect sizes (R^2 values) that provide a marker of the magnitude of the reversal effect of each adenosine antagonist when coadministered with a DA antagonist. These calculations were performed on the lever pressing data from published papers [78], as well as unpublished data [Nunes EJ, Randall PA, Santerre JL *et al.*, Unpublished Data]. These analyses were conducted by removing the vehicle plus vehicle control data, and calculating the R^2 value for the four treatments that included a DA antagonist injection alone as well as the DA antagonist combined with an adenosine antagonist. With this type of calculation, the magnitude of the treatment effect is independent of the number of animals, and is expressed as the proportion of total variance accounted for by treatment variance (e.g., $R^2 = 0.3$ reflects 30% of the variance explained across experiments and measures; larger effect sizes mean greater reversal effects).
CPT: 8-cyclopentyltheophylline; DA: Dopamine; DCPCX: 8-cyclopentyl-1,3-dipropylxanthine.

These findings indicate that there is a relatively selective interaction between antagonists of DA D_2 and adenosine A_{2A} receptors (Figure 2). Recently, it was demonstrated that either systemic or intra-accumbens injections of the adenosine A_{2A} receptor antagonist MSX-3 reversed the effects of intra-accumbens injections of the D_2 antagonist eticlopride on effort-related choice [84], demonstrating that nucleus accumbens is an important locus for this D_2–A_{2A} interaction. Moreover, these results from studies of effort-related choice behavior are consistent with the large body of evidence demonstrating that A_{2A} antagonism can generally reverse the effects of D_2 antagonism across a wide range of behavioral contexts, including tasks that involve functions related to ventral and dorsal striatum [115,116,124,125]. The specificity of this interaction is possibly related to the pattern of cellular localization of adenosine A_1 and A_{2A} receptors in striatal areas, including the nucleus accumbens [103]. Adenosine A_{2A} receptors are located on enkephalin-positive striatal neurons that also express DA D_2 receptors [98,100,103,106,126]. DA D_2 and adenosine A_{2A} receptors are able to form heteromeric complexes, in which the two receptors become linked and display alterations in their binding characteristics, and these receptors also converge onto the same cAMP-related signal transduction pathways [103–105,107,108,127–129]. Thus, adenosine A_{2A} antagonists may be so effective at reversing the actions produced by DA D_2 antagonists because they reverse the basic cellular manifestations of D_2 blockade. Consistent with this hypothesis, recent studies have employed c-Fos immunoreactivity to provide a cellular marker of the interaction between DA D_2 and adenosine A_{2A} receptors. These experiments have demonstrated that doses of adenosine A_{2A} antagonists that are effective at reversing the actions of DA D_2 antagonists on tremor and effort-related choice behavior can also reverse the D_2-antagonist-induced enhancement of c-Fos expression in ventrolateral neostriatum [130] and nucleus accumbens core [84], respectively. However, despite the colocalization of DA D_1 and adenosine A_1 receptors on

the same striatal neurons [103], injections of the A_1 antagonists DPCPX and CPT failed to reverse the behavioral effects of the DA D_1 antagonist ecopipam [Nunes EJ, Randall PA, Santerre JL *et al.*, Unpublished Data].

In summary, research over the last few years has begun to identify components of the brain circuitry involved in effort-related processes. Nucleus accumbens DA and adenosine interact to regulate effort-related choice behavior, and other structures, such as basolateral amygdala and prefrontal/anterior cingulate cortex, are also involved. Figure 3 provides an outline of the forebrain circuits that participate in effort-related functions. Recent research employing a combination of behavioral, anatomical, neurochemical and pharmacological methods has contributed to our understanding of the interactions that occur between different components of this circuitry. Using 'disconnection' methods, Floresco and Ghods-Sharifi demonstrated that unilateral inactivation of the basolateral amygdala on one side of the brain, combined with contralateral inactivation of the anterior cingulate cortex, substantially altered performance on the T-maze barrier choice task [97]. These findings support the hypothesis that serial transfer of information between these structures is involved in effort-related decision making. A similar conclusion was reached by Hauber and Sommer [131], who reported that unilateral cell body lesions of anterior cingulate cortex combined with contralateral cell body lesions of nucleus accumbens can also change effort-based decision making in rats responding on the T-maze task. Another part of this circuitry appears to be the ventral striatopallidal pathway. Neurons originating in nucleus accumbens core areas that have been implicated in effort-related processes project to the lateral ventral pallidum [121,132]. The cell bodies of many of these neurons also contain adenosine A_{2A} receptors [121]. This projection is GABAergic, and recent evidence indicates that extracellular levels of GABA, as measured by microdialysis, were increased by local accumbens core injections of either the adenosine A_{2A} agonist CGS 21680 [121] or the DA D_2 antagonist eticlopride (Figure 4) at doses that also produce the shift from lever pressing to chow intake in rats responding on the operant concurrent choice task. Consistent with this observation, it was reported that injections of the $GABA_A$ agonist, muscimol, directly into the ventral pallidum also decreased lever pressing and increased chow intake [132], while injections of muscimol into a control site dorsal to the ventral pallidum were ineffective. Moreover, injections of the adenosine A_{2A} agonist CGS 21680 into nucleus accumbens on one side of the brain, combined with muscimol injected into the ventral pallidum on the contralateral side, reduced lever pressing in rats responding on a VI 60 s schedule that had an additional work requirement (FR10) attached [121]. This effect is very similar to that previously reported to occur after accumbens DA depletions [68].

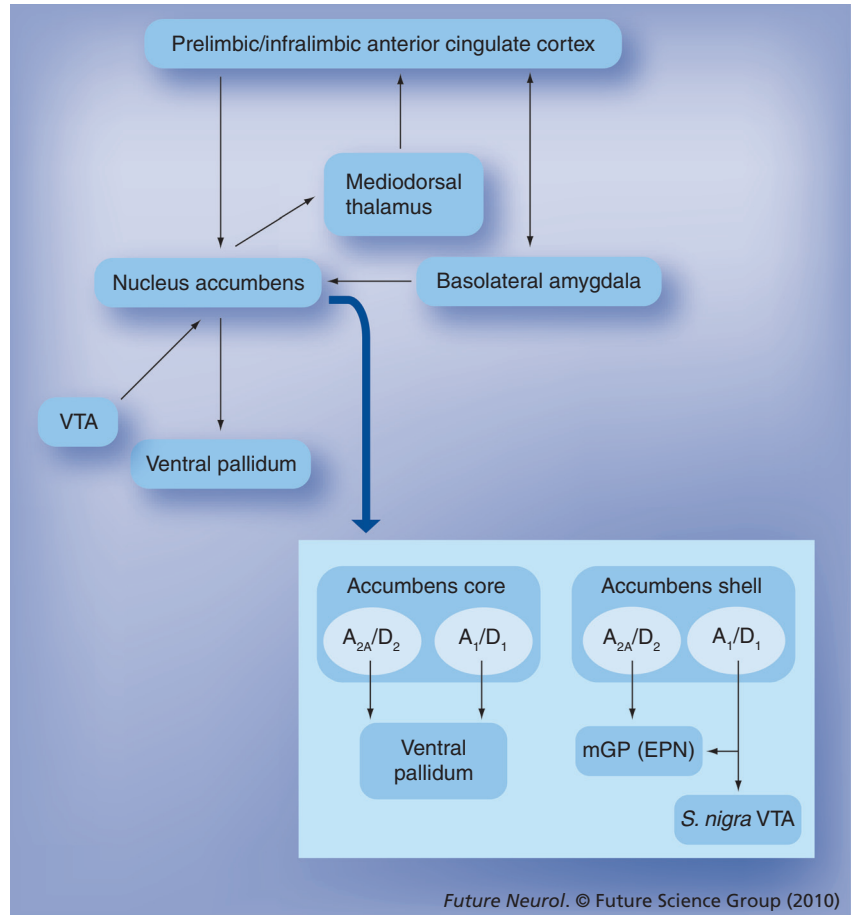

Figure 3. Forebrain circuits involved in effort-related functions.
Top: Anatomical circuit diagram showing the connections between nucleus accumbens and other brain interconnected brain areas (frontal/cingulated cortex, amygdala and pallidal areas) that are involved in the regulation of behavioral activation and effort-related decision making. Lower right (see arrow): enhanced view of nucleus accumbens showing localization patterns for dopamine and adenosine receptors.
EPN: Entopeduncular nucleus; mGP: Medial globus pallidus; *S. nigra*: *Substantia nigra*; VTA: Ventral tegmental area.

Clinical significance

In addition to contributing to the basic scientific understanding of brain mechanisms related to aspects of motivation, studies of effort-related processes also have substantial clinical implications. In her book *Manic*, Cheney describes her own subjective experience of mania in the following terms: "increased energy: during

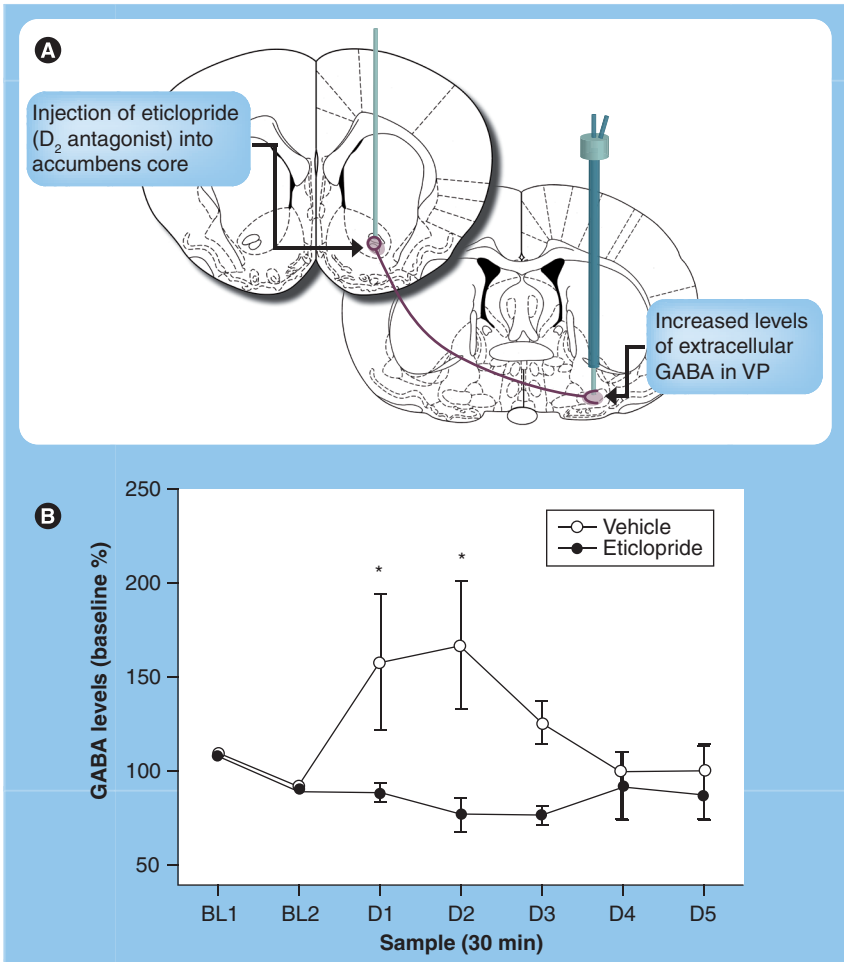

Figure 4. D_2 blockade in nucleus accumbens increases GABA release in ventral pallidum. (A) Diagram showing the placement of a drug injection cannula in nucleus accumbens, and a microdialysis probe in the ipsilateral ventral pallidum. For these studies [Farrar, unpublished doctoral dissertation, University of Connecticut, 2009], either 4.0 µg of the D_2 antagonist eticlopride (n = 7) or saline vehicle (n = 8) was injected into the nucleus accumbens core (1.0 µl total volume). The dialysis samples obtained from ventral pallidum were collected over successive 30-min periods and were analyzed using high-performance liquid chromatography with electrochemical detection. These microdialysis and neurochemical methods have been published previously [124]. Rat brain coronal sections were modified from [133]. **(B)** Graph showing the effect of eticlopride injection on extracellular GABA, with data expressed as a percentage of baseline. This graph includes data (mean + standard error of the mean) from the last two baseline preinjection samples (BL1–2), and the five samples after injection, for groups treated with eticlopride or vehicle (D1–5; the arrow in **(A)** indicates point of injection). Analysis of variance revealed that there were no group differences in the raw GABA levels of the baseline samples ($F[1,13] = 0.014$; not significant), nor was there a difference between the first and second baseline samples ($F[1,13] = 4.42$; not significant). Infusion of eticlopride into accumbens core significantly increased levels of extracellular GABA in ventral pallidum. Analysis of variance revealed a significant effect of drug treatment ($F[1,13] = 8.02$; $p < 0.05$) and a significant treatment by sample interaction ($F[6,78] = 3.54$; $p < 0.05$). Non-orthogonal planned comparisons revealed that the eticlopride-treated group had significantly elevated VP GABA levels at the first and second postinjection samples (*$p < 0.05$). Furthermore, orthogonal analysis of trends across all seven samples for the percentage baseline data demonstrated a significant sample X treatment interaction for the quadratic trend ($F[1,13] = 7.20$; $p < 0.05$), indicating that ventral pallidal GABA levels in the eticlopride-treated group showed an increase followed by a decrease, whereas GABA levels for the vehicle group did not.
VP: Ventral pallidum.

manic episodes, I can zip through all the work I couldn't touch while I was depressed" [133]. Although depression is defined as an affective disorder, with symptoms that include mood alterations and negative affect, some of the most common symptoms of depression are energy-related dysfunctions such as slowness, tiredness, listlessness and apathy [134,135]. Sometimes referred to as psychomotor slowing or retardation, anergia or fatigue, this cluster of symptoms can be a debilitating feature of major depressive disorder, and can also be present in other psychiatric and neurological conditions [134–157].

The neural basis of the impaired psychomotor function presented in major depressive disorder is still being characterized. Nevertheless, considerable evidence implicates central DA, basal ganglia and cortical mechanisms [11,140–145]. Caligiuri and Ellwanger suggested that DA transmission could play an important role in the expression of psychomotor slowing in depression [142]. Schmidt *et al.* observed that reduced DA transmission in psychiatric patients was not related to anhedonia, but instead was related to decreased interaction with the environment and psychomotor slowing [144]. The efficacy of several antidepressant drugs for reversing psychomotor slowing in depressed patients was related to the ability of these drugs to inhibit DA uptake [145]. Stimulants that enhance DA transmission have also been used to treat energy-related symptoms in depressed individuals [136]. Antiparkinsonian drugs such as L-DOPA and bromocriptine have mixed antidepressant characteristics with regard to other symptoms of depression, but they do tend to improve anergia [141]. Imaging studies also have implicated the basal ganglia structures, as well as interconnected brain areas such as prefrontal cortex and anterior cingulate cortex, in psychomotor slowing in depression [146,147].

In addition to being a feature of major depressive disorder, energy-related dysfunctions are often observed in patients with other psychiatric or neurological conditions. Moreover, as is the case with major depression, the anergia, apathy and fatigue observed in these patients appears to involve DA systems and basal ganglia mechanisms. There are several reports of energy-related problems, typically labeled fatigue, in patients with Parkinson's disease [152]. These patients describe their loss of energy by statements such as "my energy bubble just bursts" and "it's like my battery runs down" [152]. Caligiuri and Ellwanger compared

motor function in depressed patients and those with parkinsonism [142], and observed that motor slowing in depression is behaviorally quite similar to parkinsonian bradykinesia. They suggested that motor slowing in depression and parkinsonism could result from common underlying mechanisms. Psychomotor slowing is often observed during withdrawal from stimulant addiction, and it was the psychiatric symptom most strongly associated with reduced levels of striatal DA transporter density in a PET study of methamphetamine abusers in withdrawal [143]. Furthermore, there are individuals who have a severe motivational disturbance that has been labeled as anergia, or apathy, yet these individuals do not meet the diagnostic criteria for depression [148,149]. Energy-related symptoms in these people can be ameliorated with the DA agonist bromocriptine, and it has been suggested that DA is involved in this type of syndrome [148,149]. The DA uptake inhibitor buproprion improved apathy symptoms in patients with organic brain disease [150]. Loss of drive or motivation and a lack of initiation of spontaneous activities was reported to be improved by administration of the antiparkinsonian DA agonist bromocriptine in patients who had either traumatic brain injury or subarachnoid hemorrhage [151]. Another disorder associated with energy-related symptoms such as fatigue is multiple sclerosis [152,153]. Fatigue in multiple sclerosis has been described as "a feeling of physical tiredness and lack of energy distinct from sadness or weakness" [154]. Basal ganglia mechanisms have been implicated in multiple sclerosis-related fatigue [155], and drugs that act on DA such as pemoline and buproprion have been used to treat this symptom [153,156]. Furthermore, HIV patients can also show apathy, and a recent morphometric study demonstrated that this apathy in HIV patients is accompanied by reductions in nucleus accumbens volume [157].

It is evident from the review of the animal research provided above that adenosine A_{2A} receptor antagonists could represent novel therapeutic targets for the treatment of energy-related symptoms in humans. At present, a number of these drugs are being developed as treatments for idiopathic Parkinson's disease. As fatigue is often a feature of Parkinson's disease [152], the next generation of studies could provide a unique opportunity to investigate the ability of adenosine A_{2A} antagonists to improve energy-related symptoms. Additional research should also focus on the effects of adenosine A_{2A} antagonists on psychomotor slowing and fatigue in patients treated with antipsychotic drugs, as well as people with multiple sclerosis, depression or other disorders. For all these studies, it will be useful to place emphasis on the continued development of both self-report and behavioral assessment tools, in order to characterize the symptoms and measure their responsiveness to treatment.

Conclusion

In summary, there are multiple components of the forebrain circuitry regulating behavioral activation and effort-related processes. One nodal point in this circuitry is the DA innervation of nucleus accumbens [11,13,77,85,158]. Low systemic doses of DA antagonists, local injections of DA antagonists into nucleus accumbens and neurotoxic depletion of accumbens DA, all produce a condition that results in lower behavioral activation and decreased output of food-motivated instrumental behavior, particularly when the instrumental response has a substantial work requirement. These actions occur despite the fact that these manipulations have little or no effect on appetite for food, or primary or unconditioned food motivation [13]. In addition, DA manipulations produce a bidirectional modulation of effort-related choice behavior. Decreasing accumbens DA transmission biases animals towards lower-effort alternatives, although these animals remain directed towards the acquisition and consumption of the primary motivational stimulus [11,13,158]. By contrast, increasing DA transmission has been demonstrated to increase selection of high-effort alternatives [79,87]. Along with nucleus accumbens, additional components of this circuitry in animals and humans include prefrontal/anterior cingulate cortex, basolateral amygdala and ventral pallidum [93,131,159–161]. Furthermore, DA interacts with the purine neuromodulator adenosine, particularly in the nucleus accumbens, to regulate effort-related functions [13,77,85,158]. Adenosine A_{2A} agonists injected into nucleus accumbens can mimic the effects of DA depletion or antagonism, while adenosine A_{2A} antagonists can attenuate the effort-related behavioral effects of DA D_2 antagonists.

As well as providing basic science information regarding a fundamental aspect of normal motivation, research in this area can also yield insights into pathological aspects of motivation in humans [134]. Symptoms such as anergia, psychomotor slowing, apathy and fatigue, which

represent conditions in which there are abnormally low levels of behavioral activation, are frequently observed in patients with depression and other psychiatric and neurological disorders. Subjectively, patients with these symptoms report a lack of energy, and research indicates that there are also profound behavioral manifestations that can be maladaptive and debilitating. The severity of these psychomotor or energy-related symptoms is related to problems with social function and employment, as well as treatment outcomes [162]. Importantly, an examination of the basic science and clinical literature indicates that there are noteworthy similarities between the brain circuitry and neurochemical systems that have been implicated in effort-related processes in animals and those involved in pathological aspects of behavioral activation in humans [11,134]. These observations suggest that basic research on animals can yield critical insights into the neural underpinnings of energy-related dysfunctions in humans, and that such research could ultimately lead to novel treatments for these disorders. For example, it is possible that adenosine A_{2A} receptor antagonists that are currently being developed for their antiparkinsonian effects could be beneficial for treating energy-related symptoms in humans [11,119,163].

Future perspective

As previously described, in most animal studies adenosine A_{2A} receptor antagonists appear to be more effective at reversing the effects of D_2 antagonists than they are at reversing the effects of D_1 antagonists. This will have to be investigated more thoroughly in humans, but it could have implications for the development of these compounds as clinical tools. As DA depletions result in a lack of D_1 as well as D_2 receptor stimulation, it may be that adenosine A_{2A} antagonists will have limited efficacy in treating patients with idiopathic Parkinson's disease. As previously described, adenosine A_{2A} receptor antagonists appear to have more direct effects on the medium spiny cells that also contain D_2 receptors, but their ability to interact with so-called direct pathway neurons, which are more likely to contain D_1 receptors, may be somewhat limited. For these reasons, it would be useful to consider combination treatments that include drugs that act on other parts of the striatal circuitry, which are less influenced by the effect of adenosine A_{2A} receptor blockade; such treatments could include D_1 agonists or muscarinic M4 antagonists [131]. This strategy could yield benefits for the treatment of motor symptoms of Parkinson's disease, but could also be advantageous for the treatment of energy-related symptoms as well.

Executive summary

Diverse aspects of motivation

- Directional aspects: behavior is directed towards or away from stimuli.
- Activational aspects: motivated behavior is characterized by a high degree of vigor, persistence and effort.

Dopaminergic involvement in behavioral activation & effort

- Low doses of dopamine (DA) antagonists, as well as accumbens DA depletions or antagonism, do not impair appetite for food or primary food motivation. It is overly simplistic to label nucleus accumbens DA as a 'reward' or 'pleasure' system.
- Interference with DA transmission impairs activational aspects of motivation, making it less likely that animals will work for stimuli such as food.
- Interference with accumbens DA transmission affects effort-related decision making, biasing animals towards low-effort alternatives.

Dopamine & adenosine interact in the regulation of effort-related processes

- Adenosine A_{2A} agonists, when injected into the accumbens, produce effects that resemble those of accumbens DA depletion or antagonism.
- Adenosine A_{2A} antagonists reverse the effort-related effects of DA antagonists, while A_1 antagonists are relatively ineffective.
- There is a very specific interaction between DA D_2 and adenosine A_{2A} receptors, which is probably related to the colocalization of these receptors in the same population of medium spiny neurons.
- The nucleus accumbens is an important locus at which DA D_2 and adenosine A_{2A} receptors interact in order to regulate effort-related processes.
- Effort-related output from the nucleus accumbens to related forebrain circuits appears to be conveyed by the GABAergic ventral striatopallidal pathway.
- The broader forebrain circuitry involved in effort-related processes includes the anterior cingulate cortex and basolateral amygdala.

Clinical implications

- Animal research on behavioral activation and effort-related decision making may provide insights into the neurochemistry and pharmacology of effort- or energy-related symptoms, such as psychomotor slowing, anergia, apathy and fatigue, which are seen in various psychiatric and neurological disorders.

Future perspective

- Adenosine A_{2A} receptor antagonists may be useful for the treatment of energy-related symptoms in humans.

In view of the apparent specificity of the interaction between DA D_2 and adenosine A_{2A} receptors, another potential use for adenosine A_{2A} antagonists is the treatment of the behavioral side effects, both motor and motivational, that are produced by antipsychotic drugs [115,116,119]. The vast majority of antipsychotic drugs are D_2 antagonists, and the therapeutic utility of these compounds is directly related to actions on the D_2 receptor family, as opposed to the D_1 receptor family. Thus, in view of the consistent findings in the animal literature that demonstrates that adenosine A_{2A} antagonists readily reverse the actions of D_2 antagonists, clinical studies assessing this effect need to be conducted. Of course, in order to be clinically useful, the question of whether or not adenosine A_{2A} antagonists also reverse the therapeutic effect of antipsychotics needs to be addressed. Such research would not only be necessary from a practical standpoint, but it would also have an added benefit, in that it would test one of the recent theories of antipsychotic action. Although many researchers have maintained that the therapeutic and behavioral side effects of antipsychotic drugs result from actions on distinct mechanisms, it has recently been suggested that the therapeutic effect of D_2 antagonists is a result of actions on subcortical dopaminergic mechanisms, including those in nucleus accumbens, which are involved in aspects of motivation such as motivational salience and arousal [164]. Thus, research in this area could afford a valuable opportunity that would have both clinical and theoretical implications. If adenosine A_{2A} antagonists can reverse the motivational effects of D_2 antagonists, but leave the therapeutic antipsychotic effect intact, then it would indicate that these effects are actually a result of actions on distinct and dissociable mechanisms. Moreover, such a finding would promote the development of novel clinical tools for the treatment of pathological aspects of motivation.

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