

Striatal Dopamine D2 Receptors Regulate Cost Sensitivity and Behavioral Thrift

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Abstract—The role of the dopamine D2 receptor (D2R) in regulating appetitive behavior continues to be controversial. Earlier literature suggests that reduced D2R signaling diminishes motivated behavior while more recent theories suggest that reduced D2R, as has been putatively observed in obesity, facilitates compulsive appetitive behavior and promotes overeating. Using a homecage foraging paradigm with mice, we revisit classic neuroleptic pharmacological studies from the 1970s that led to the ‘extinction mimicry’ hypothesis: that dopamine blockade reduces reinforcement leading to an extinction-like reduction in a learned, motivated behavior. We complement this with a selective genetic deletion of D2R in indirect pathway medium spiny neurons (iMSNs). Administration of haloperidol shifts foraging strategy toward less effortful, more thrifty pursuit of food without altering consumption or bodyweight. D2R deletion in iMSNs also reduces effort and energy expended toward food pursuit, but without a compensatory shift in foraging strategy, resulting in loss of body weight, an effect more pronounced under conditions of escalating costs as the knockouts fail to adequately increase effort. The selective knockouts exhibit no change in sucrose preference or sucrose reinforcement. These data suggest that striatal D2R regulates effort in response to costs, mediating cost sensitivity and behavioral thrift. In the context of obesity, these data suggest that reduced D2R is more likely to diminish effort and behavioral energy expenditure rather than increase appetitive motivation and consumption, possibly contributing to reduced physical activity commonly observed in obesity. © 2019 IBRO. Published by Elsevier Ltd. All rights reserved.

Key words: dopamine D2 receptor, neuroeconomics, indirect pathway, D2R selective knockout, extinction mimicry, behavioral energy expenditure.

INTRODUCTION

In recent years, there has been increased focus on the role of sedentary behavior in obesity (Chaput et al., 2011; Ladabaum et al., 2014; Shook et al., 2015), with evidence suggesting voluntary activity is reduced in obesity, an effect that can persist even after weight loss (Kravitz et al., 2016). While caloric intake is the prime determinant of body weight in the short-term (Tataranni et al., 2003; Luke et al., 2008; Westerterp and Speakman, 2008; Luke and Cooper, 2013 but see Church et al., 2011), physical activity contributes to long-term maintenance of weight loss, reducing cycles of weight loss and rebound weight gain (Levin and Dunn-Meynell, 2004; MacLean et al., 2009, 2015; DeLany et al., 2014). Moreover, exercise is important for health. Sedentary lifestyles has been associated with

increased rates of chronic illness and mortality imposing a significant global economic burden (Healy et al., 2011; Ding et al., 2016). Adaptations in response to increased physical activity suggest that total energy expenditure may be regulated and constrained within limits (Pontzer et al., 2016), perhaps analogous to the notion of a set-point in body weight regulation. How energy expenditure and physical activity are regulated is poorly understood, but such understanding is important in designing interventions aimed at increasing physical activity, both in the treatment of individuals and at a broader population level.

Midbrain dopamine is a key neural substrate mediating addiction (Berke and Hyman, 2000; Di Chiara et al., 2004; Kenny et al., 2013; Pascoli et al., 2015; Volkow et al., 2017). More recently, dopamine has been suggested to play a role in compulsive overeating associated with obesity (Volkow et al., 2011; Blum et al., 2014; Guo et al., 2014; Naef et al., 2015). Widely associated with compulsive reward seeking, DA is also known to regulate voluntary activity (Beeler et al., 2012a). Though both increased caloric intake and reduced activity contribute to positive energy balance and obesity, the potential role of

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Abbreviations: ANOVA, analysis of variance; D2R, dopamine D2 receptor; iMSNs, indirect pathway medium spiny neurons.

dopamine in the latter has been considerably less examined.

The dopamine D2 receptor (D2R) has been a focus of attention in obesity studies (Volkow et al., 2011; Kenny et al., 2013). Initial reports that D2R was reduced in obesity (Wang et al., 2001) gave rise to the ‘reward deficiency’ hypothesis that suggested animals and people compulsively pursue reward, such as palatable foods, to induce dopamine release to compensate for reduced D2R signaling (Volkow and Wise, 2005; Kenny, 2011; Blum et al., 2014). Subsequent studies have yielded contradictory results (Volkow et al., 2008; de Weijer et al., 2011; Kessler et al., 2014; negative: Dunn et al., 2012; Eisenstein et al., 2013; de Weijer et al., 2014; Cosgrove et al., 2015; Karlsson et al., 2015; Tuominen et al., 2015). Similarly, the reduced function D2R variant Taq1A has been frequently associated with obesity (Barnard et al., 2009; Chen et al., 2012; Carpenter et al., 2013), though a recent large, prospective study did not find any association (Hardman et al., 2014). None of these studies, however, have examined changes in physical activity potentially associated with reduced D2R, despite the known role dopamine and D2R in regulating activity (Beeler et al., 2012a; Kravitz et al., 2016; Beeler and Mourra, 2018).

Earlier studies using pharmacological blockade of D2R suggested that reduced D2R signaling diminished rather than increased appetitive motivation (Salamone et al., 2007; Wise, 2008). In classic studies in the 1970s and 80s, Wise and colleagues (Wise et al., 1978; Wise, 2008) administered neuroleptics (predominantly antagonizing D2R) to rats well-trained in an operant task. Rather than observing an immediate effect on their motivation to lever press, a decrease in effort was observed progressively across days, interpreted that dopamine was mediating reinforcement learning. The progressive decrease across days has been called ‘extinction mimicry.’ Here we revisit these classic studies in a homecage foraging paradigm and further investigate the role of D2R regulating consumption and activity using mice with a selective deletion of D2R in indirect pathway medium spiny neurons (iMSNs) (Friend et al., 2016). We demonstrate that reduced D2R signaling shifts behavioral strategy toward greater cost sensitivity and behavioral energy conservation. We suggest that D2R regulates costs by gating the degree to which dopamine release can disinhibit the indirect pathway.

EXPERIMENTAL PROCEDURES

Animals

For haloperidol studies, wild-type C57BL/6 mice of both sexes were used at approximately 120 days of age. To generate the D2R iMSN KO mice, mice expressing cre-recombinase regulated by the adenosine 2A receptor promoter (Adora2a; B6.FVB(Cg)-Tg(Adora2a-Cre)K G139Gsat/Mmudc; GENSAT, 036158-UCD) were crossed with mice carrying a conditional *Drd2* null alleles (B6.129S4 (FVB)-*Drd2*^{tm1.1Mrub}/J, JAX 020631, hereafter *fdrd2*) and bred to homozygosity for the *Drd2* null allele, with either *cre*^{+/−} (experimental animals) or

cre^{−/−} (littermate controls), as in Friend et al. (2016). The ablation of D2R in iMSNs with these genotypes have been previously validated in published accounts (Dobbs et al., 2016; Friend et al., 2016; Lemos et al., 2016). Genotypes were verified using PCR. For experiments, mice were singly housed in homecage operant chambers (below) and maintained on 12:12 light–dark cycles with ad libitum access to water. All procedures were approved by the Queens College Institutional Animal Care and Use Committee.

Behavioral tests

Homecage operant paradigms: mice were singly housed in standard mouse polycarbonate mouse cages equipped with two levers, pellet dispenser and food hopper (Med-Associates, Fairfax, VT, USA). No food restriction was employed and the only source of food was through lever pressing (closed economy) except in the concurrent choice test. 20 mg grain pellets (Bio-Serv, Flemington, NJ, USA) were dispensed on a progressive ratio schedule with an increment of two such that the first pellet cost 2 lever presses, the next 4, the next 6 and so on (PR2). After 30 min of inactivity (no lever press on active or inactive lever), the ratio reset to 2 to start the sequence again. This allows the mice to titrate their average cost per pellet by balancing the size of meals (with larger meals proportionally more expensive) against the number and frequency of meals (Fig. 1A). In the homecage concurrent choice, mice were provided free chow in their cage and could earn sucrose pellets (Bio-Serv, Flemington, NJ) through lever pressing on a PR2 schedule. In experiments with running wheels, radio-telemetry running wheels (Med-Associates, Fairfax, VT) were fit in the operant-equipped cages and running was monitored 24/7 in 1 min bins.

Open field: mice were tested in a rat-sized open field (40 cm long × 40 cm wide × 37 cm high) using photobeams to detect and quantify movement (Med-Associates, Fairfax, VT). Three 90-min sessions on consecutive days were averaged.

Sucrose preference: mice were singly housed and provided with three bottles, one containing water and two containing sucrose at concentrations that increased across days with each concentration applied for two days. The position of the bottles were switched daily to counter-balance for any side preference. Consumption was measured daily.

Two-bottle conditioning: Mice were habituated to the test chambers for three days, 30 min per day. For training, mice were placed in chambers with a single bottle containing either water or 0.8 M sucrose located in the center of the chamber wall. Water and sucrose tubes marked with either white or red tape around the sipper to serve as differentiating cues, counter-balanced between the tastants. Mice were exposed to tastant for 60 min sessions with sucrose and water on alternating days for a total of 6 training days, 3 for each tastant. On test day, mice were placed in the chambers for 10 min with both sucrose- and water-cued bottles on either side of the cage, both containing water. Preference is calculated as the amount consumed on test day from

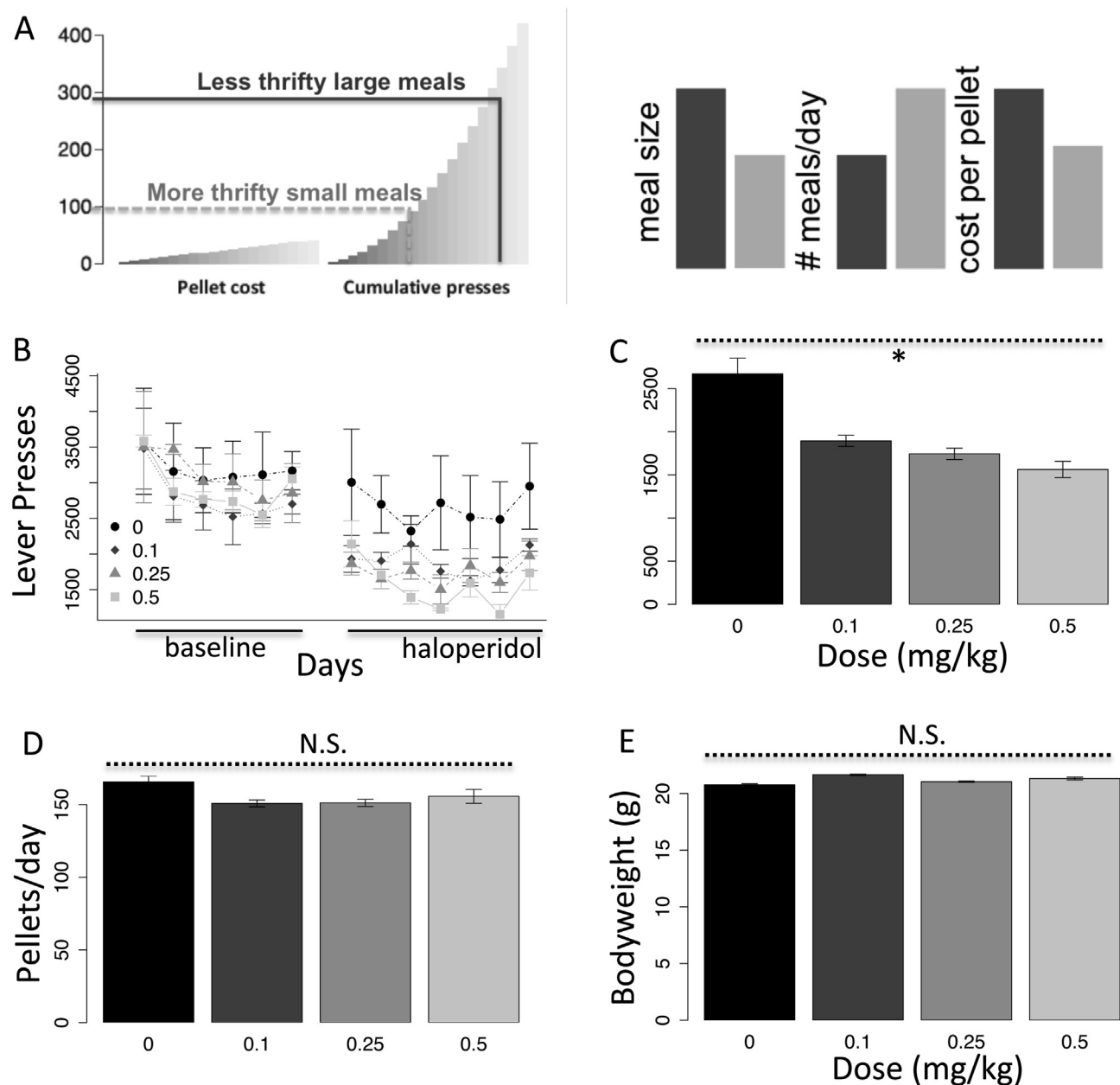


Fig. 1. Haloperidol decreases responding without altering consumption or body weight. **(A)** Illustration of thrift in homecage PR paradigm comparing more and less thrifty strategies in balancing meal size and frequency, **(B)** Dose-response effect of haloperidol on active lever presses showing 6 days of pre-treatment baseline and 7 days of haloperidol administration at the indicated doses. **(C)** Average responding across treatment days by dose (black bar represents average baseline across groups). **(D)** Average consumption by dose (black bar, baseline), **(E)** Average body weight by dose (black bar, baseline). $N = 6$. * $p < .05$. Error bars, S.E.M.

the sucrose-paired bottle divided by consumption from both bottles.

Drugs

Pharmaceutical grade haloperidol solution was diluted in saline to indicated concentrations prior to 1× daily intraperitoneal administration at 5:30 pm, 30 min prior to onset of active cycle.

Fitting data to exponential demand function

The data from each mouse was individually fit and plotted and used to calculate averages of elasticity coefficient for

the two genotypes tested. Additionally, the genotype data were fit by group to generate the average fit. We used the exponential demand function of Hursh and Silberberg (2008) as follows:

$$demand = Q + k(e^{\alpha p} - 1)$$

where Q is maximal consumption estimated at zero cost, k sets the range (here, $k = 1$), p is the price (cost in lever presses) set as the progressive ratio *increment* active during each day (i.e., PR2, PR4, PR6 etc.) and α is the elasticity coefficient. The data were fit in R (<https://www.r-project.org>, v. 3.4.3) minimizing least squares

using *Isqcurvefit* in package *pracma* (v. 2.1.1) with Q and alpha as free parameters, with initial parameters set to $\log_{10}(150)$ for Q and 0.0012 for alpha.

Statistics

Analysis of variance (ANOVA) was used to test significance using R (v. 3.4.3). Error bars represent standard error of the mean (S.E.M.).

RESULTS

Haloperidol reduces effort without altering consumption or bodyweight

To revisit extinction mimicry studies, we used a homecage operant paradigm (Beeler et al., 2012b). In this closed-economy, mice obtained food on a progressive ratio schedule (HCPR-2, see Experimental procedures) with the cost resetting if the mouse stops pressing for 30 min (end of a bout of pressing or ‘meal’). Under these contingencies, larger meals are more costly, but mice can maintain equivalent consumption with less effort by eating shorter but more frequent meals (Fig. 1A). For example, hyperdopaminergic mice eat larger but fewer meals and, as a consequence, exert much more effort for the same total amount of food, reflected in a higher average cost per pellet (Beeler et al., 2012b,c).

Wild-type C57BL/6 mice were allowed to establish stable pressing (Fig. 1B, left) before haloperidol administration for seven days (Fig. 1B, right). No baseline differences were observed between groups ($F_{(1,10)} = 0.17$, $p = .69$). Haloperidol induced a dose-dependent reduction in lever pressing (Fig. 1B, C, dose, $F_{(1,10)} = 6.02$, $p < .05$), though we did not observe a gradual, progressive decrease in pressing. Despite clear reduction in lever pressing, consumption was not significantly reduced (Fig. 1D, $F_{(1,10)} = 0.72$, $p = .41$) and there was no change in body weight (Fig. 1E, $F_{(1,10)} = 0.39$, $p = .54$). Though haloperidol does not impair motor capacity for lever pressing, it can slow the rate of pressing (Salamone et al., 1993). In a conventional, time-limited session-based paradigm, this could lead to conflating decreased consumption with slower pressing. In the homecage paradigm, however, there are no time limits and so reduced rate of pressing is not conflated with motivation: the mice can take as much time as they need.

Haloperidol dose-dependently induces greater behavioral thrift

To examine how mice reduced their effort but maintained consumption and bodyweight, we analyzed meal patterns. Upon administration of haloperidol, mice decrease the size (and cost) of individual meals (Fig. 2A, $F_{(1,10)} = 6.12$, $p < .05$) but compensate by increasing the frequency and number of meals (Fig. 2B, $F_{(1,10)} = 10.76$, $p < .01$), such that a decreased breakpoint (Fig. 2C, $F_{(1,10)} = 6.15$, $p < .05$) results in overall lower average cost per pellet (Fig. 2D, $F_{(1,10)} = 8.64$, $p < .05$). To ensure that the maintenance

of consumption was not the result of compensatory pressing after haloperidol clearance, we plotted pressing across 24 h averaged across haloperidol days. We observe an obvious effect of haloperidol in the first half of the dark cycle that wears off in the second half; however, during this latter period there is no compensatory increased consumption (Fig. 3A). Consumption (Fig. 3B) is greater during the first half for all mice and unaffected by haloperidol, though cost-per-pellet (Fig. 3C) is decreased by haloperidol during this period of greater consumption. These data suggest haloperidol induces increased behavioral thrift, shifting to a strategy that reduces cost while sustaining similar consumption, exhibiting a pattern exactly the opposite of hyperdopaminergic mice (Beeler et al., 2012b,c).

Selective deletion of iMSN D2R induces greater behavioral thrift

D2R is ubiquitously expressed across multiple brain regions and cell types (Dobbs et al., 2017). To selectively examine the role of D2R expressed on iMSNs, we crossed floxed *drd2* mice with Adora-cre mice that express cre recombinase under the control of the A2A promoter, a strategy validated and used successfully in previously published reports (Dobbs et al., 2016; Friend et al., 2016; Lemos et al., 2016). Consistent with prior published studies of these mice as well as a global knock-down (Beeler et al. 2016), we observed substantially reduced running wheel activity (Fig. 4A, B; A, $F_{(1,8)} = 10.92$, $p < .01$; B, $F_{(1,9)} = 6.097$, $p < .05$) and reduced activity in the open field (Fig. 4 C, D; distance, $F_{(1,9)} = 7.31$, $p < .05$; ambulatory episodes, $F_{(1,9)} = 15.16$, $p < .01$; ambulatory time, $F_{(1,9)} = 13.35$, $p < .01$; resting time, $F_{(1,9)} = 11.43$, $p < .01$; velocity, $F_{(1,9)} = 0.001$, $p = .98$), confirming the reduced activity phenotype previously observed.

Mice were housed in operant homecages on the progressive ratio schedule (PR2) as above. In contrast to wild-type littermates that maintain or slightly gain weight, the D2R iMSN KO mice lose weight (Fig. 5A, $\text{geno} \times \text{day}$, $F_{(1,9)} = 8.25$, $p < .05$) and consume less (Fig. 5B, $F_{(1,9)} = 19.75$, $p < .01$). They exhibit substantially reduced lever pressing and breakpoint (Fig. 5C, D, lever presses, $F_{(1,9)} = 34.82$, $p < .001$; breakpoint, $F_{(1,9)} = 15.54$, $p < .01$) and, as a consequence maintain a much lower average cost-per-pellet than their wild-type littermates (Fig. 5E, $F_{(1,9)} = 17.07$, $p < .01$). Curiously, unlike the haloperidol studies, they do not exhibit a compensatory increase in the frequency of smaller meals. As a consequence, they weigh less than wild-type controls, consistent with prior observations with global D2R knockout mice (Kim et al., 2010). Friend et al (2016) demonstrated the D2R iMSN KO mice have no alterations in their basal metabolic rates. These data suggest that the D2R iMSN KO mice expend less energy in pursuit of food and consequently maintain a lower bodyweight when there is a procurement cost.

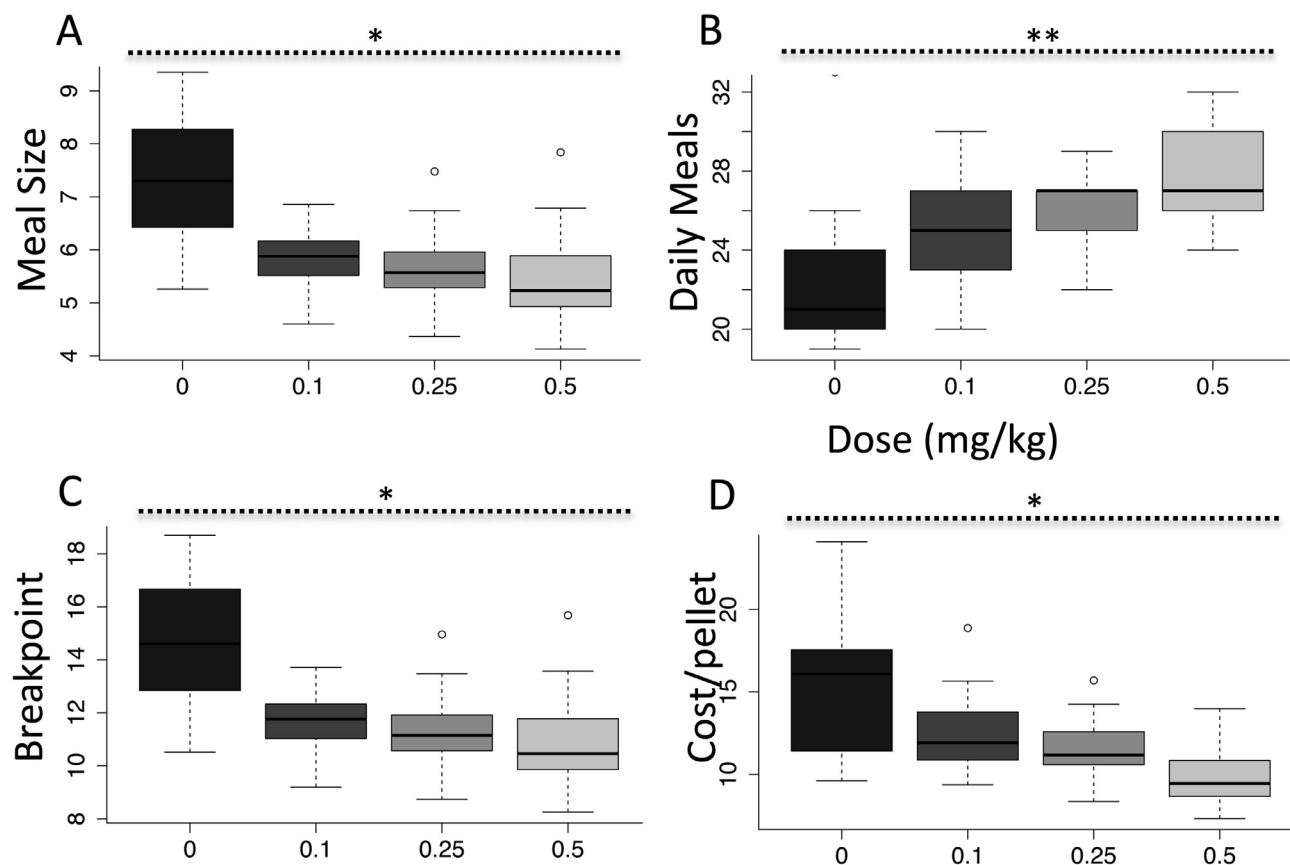


Fig. 2. Meal patterning in response to haloperidol. Dose–response (black bar indicates mean of baseline) in (A) meal size and (B) number of meals per day, (C) breakpoint and (D) average cost per pellet. $N = 6$. * $p < .05$; ** $p < .01$. Error bars, S.E.M.

Selective deletion of iMSN D2R confers greater elasticity in food demand under conditions of escalating costs and scarcity

To further probe the impact of D2R deletion in iMSNs, we placed mice in an escalating progressive ratio homepage paradigm where the increment determining the progression in pellet costs is increased each day, making food increasingly expensive across days and implementing a form of food scarcity associated with cost. All mice reduced bodyweight as food costs escalated. At higher ratios the wild-type mice increased their effort, somewhat mitigating weight loss while the D2R iMSN KO mice did not (Fig. 6A, $\text{geno} \times \text{day}$, $F_{(1,9)} = 6.45$, $p < .05$), reflecting in the wild-type ability to maintain stable consumption across cost increments while the D2R iMSN KO mice reduced their consumption with increased cost (Fig. 6B, $\text{geno} \times \text{day}$, $F_{(1,9)} = 26.52$, $p < .001$), dramatically reflected in the total lever presses per day in the two groups (Fig. 6C, $F_{(1,9)} = 21.08$, $p < .01$). This failure to respond adequately to escalating costs with increased effort is observed where both genotypes increase their breakpoint, but the increase in the KO mice is greatly diminished (Fig. 6D, geno main effect, $F_{(1,9)} = 26.1$, $p < .001$, $\text{geno} \times \text{day}$, $F_{(1,9)} = 19.47$, $p < .01$). The fact that the KO more than double their breakpoint indicates their failure to expend energy via lever pressing at lower

costs does not reflect a motor impairment. While the average cost of pellets increases nearly sevenfold for wild-type mice, the KO mice constrain these costs to only a threefold increase (Fig. 6E, $F_{(1,9)} = 23.24$, $p < .001$, $\text{geno} \times \text{day}$, $F_{(1,9)} = 16.06$, $p < .01$). The D2R iMSN KO mice do not compensate for reduced effort with increased meal frequency.

We fit consumption data to an exponential model of demand across cost increments to assess elasticity in demand (Hursh and Silberberg, 2008). The wild-type mice exhibit no elasticity, with a slight increase in demand (Fig. 7), perhaps reflecting compensatory consumption in response to increased energy expenditure to obtain pellets. In contrast, as costs escalate, the D2R iMSN KO mice reduce their demand, showing greater elasticity (Fig. 7, comparing elasticity coefficients, $F_{(1,10)} = 24.88$, $p < .001$). The strong inelasticity observed in the wild-type may seem anomalous; however, it should be noted that because this is progressive ratio, the mice experience a range of prices in every meal. In this situation, 'price' is a moving target and demand can be construed as response to the average cost of pellets across a 24 h period. In this case, the average cost per pellet in wild-type asymptotes at approximately 70 lever-presses (Fig. 6E). In more traditional paradigms with escalating fixed ratio costs, the drop in demand is modest at this cost range (e.g., Soto et al., 2011; Beeler et al., 2012b); the effect may be further reduced in progressive ratio where

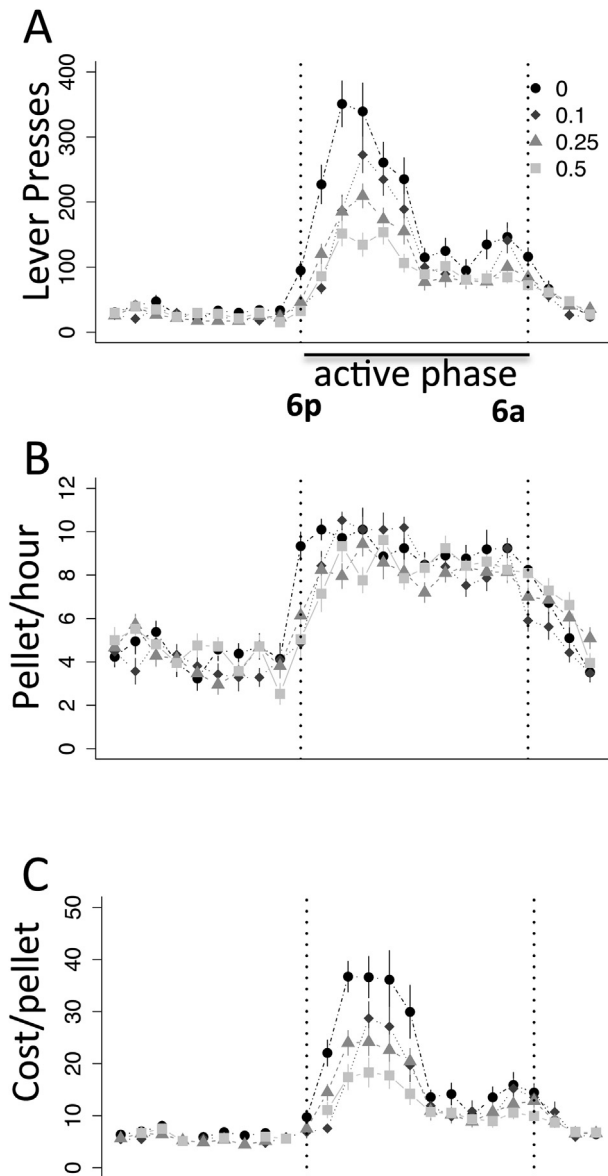


Fig. 3. Haloperidol effects on food pursuit across 24 h period. All haloperidol days were average and plotted binned by hour, showing (A) lever pressing, (B) pellets earned and (C) average cost per pellet. Statistics on dose effects presented in Figs. 2 and 3. $N = 6$. Error bars, S.E.M.

a substantial proportion of pellets are acquired at low cost such that overall demand is only modestly impacted by higher costs further in the incrementing progression. In these circumstances, the elasticity observed in the D2R iMSN KOs is even more notable.

Selective deletion of iMSN D2R has no impact on sucrose preference or reinforcement

Reduced lever pressing effort in pursuit of food described above (Figs. 5 and 6) could arise from either increased sensitivity to the cost (effortful energy expenditure in pursuit of reward) or to decreased reinforcement efficacy of the reward. To assess preference and

reinforcer efficacy, we conducted concurrent choice, sucrose preference and two-bottle conditioning tests.

In a concurrent choice paradigm, mice have free access to chow but can also choose to lever press for a more preferred food, such as sucrose pellets. In a prior study with global D2R knockdown (Beeler et al., 2016), we observed no genotype difference in lever pressing for sucrose pellets in a homecage concurrent choice paradigm. Here we tested the selective KO mice in concurrent choice and observe no difference in body weight (Fig. 8A, $F_{(1,9)} = 0.03$, $p = .86$), nor any reduction in earned sucrose pellets or breakpoint (Fig. 8A, pellets, $F_{(1,9)} = 0.1$, $p = .76$, breakpoint, $F_{(1,9)} = 0.05$, $p = .82$). These data are consistent with prior literature demonstrating that decreased dopamine function does not affect effort when costs are low (Aberman and Salamone, 1999). As all mice eat relatively little sucrose, the costs of obtaining this in a progressive ratio schedule are also relatively low. No difference between the genotypes indicates that there is no change in preference for or reinforcement efficacy of sucrose evident in this paradigm.

To test for preference in a non-effortful task, we conducted homecage sucrose preference tests. The KO mice do not exhibit any decrease in sucrose preference (Fig. 8B, $F_{(1,20)} = 0.004$, $p = .95$), suggesting the loss of iMSN D2R does not diminish how much they like sucrose or its hedonic value. In a two-bottle conditioning task, the KO do not exhibit any reduction of conditioning for the bottle previously paired with sucrose (Fig. 8C, $F_{(1,18)} = 0.125$, $p = .72$), suggesting that loss of iMSN D2R does not reduce the ability of sucrose to act as a reinforcer in associative learning in these mice. Together, data in these three tests suggest that the decrease in lever pressing for food observed in the KO mice above is not the result of decreased hedonic value or a reduction in reinforcement efficacy; rather, the decrease appears to specifically reflect increased sensitivity to costs and a predisposition to conserve energy and constrain effort in pursuit of reward.

DISCUSSION

We previously demonstrated that genetically induced hyperdopaminergia causes animals to be less thrifty in their behavioral energy expenditure: increasing how hard they work for reward without altering their overall consumption (Beeler et al., 2012b). Here we demonstrate the complementary, reverse pattern, that pharmacological blockade with haloperidol, a dopamine antagonist that acts primarily on D2R, increases thriftiness, reducing effort expended in pursuit of food without altering consumption and bodyweight.

Reduced willingness to work under haloperidol administration has been demonstrated previously using conventional session-based test paradigms (reviewed in Salamone et al., 2007). In the homecage paradigm used here, the mouse can adapt its foraging strategy to minimize costs while maintaining consumption. Haloperidol shifts foraging strategy to favor shorter, less expensive bouts of lever pressing where smaller meals are compensated by an increase in the number of meals, resulting in

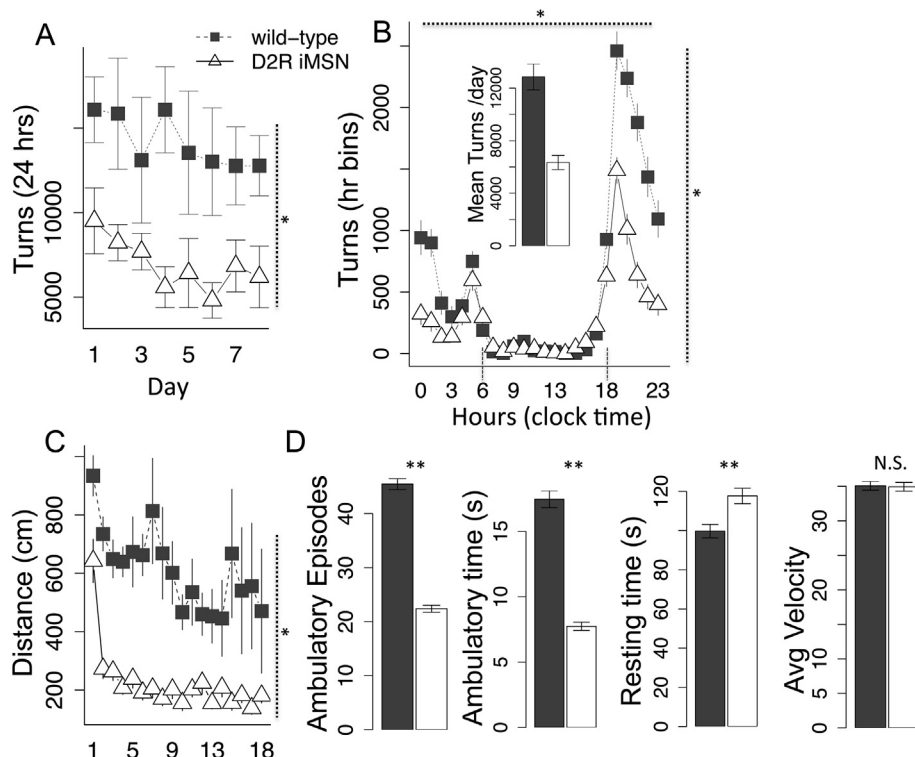


Fig. 4. Activity phenotype of D2R iMSN KO mice. (A) Total running per day across experiment, (B) running binned by hour across 24 h period (averaged across days), dotted lines demarcating active and inactive periods. Inset, total daily running averaged across experiment, (C) distance travelled in open field, (D) genotype comparison in ambulatory episodes, ambulatory time, resting time and average velocity. Vertical dotted lines indicate statistic associated with main effect while horizontal dotted line indicate genotype $\times$ repeated measure (day, hours) statistic. $N = 5$, * < 0.05 , ** < 0.01 . Error bars, S.E.M.

more economical foraging; that is, haloperidol induces greater behavioral thrift without inducing extinction or reducing consumption.

Hypothesizing that postsynaptic D2R on iMSNs specifically regulate cost sensitivity, we selectively deleted this population of D2Rs. Consistent with the haloperidol study, we observe decreased effort expended to obtain food, an effect more pronounced as costs escalate. Deletion of D2R on iMSNs confers greater demand elasticity compared to wild-type littermates. These results extend earlier findings by Soto et al. (2011) who found that mice with a global D2R knockout exhibited increased elasticity. Our data demonstrate that postsynaptic D2R on iMSNs are sufficient to mediate this effect. The D2R iMSN KO mice could compensate for smaller, less expensive meals by increasing meal number, as observed with haloperidol, but they do not; instead, they reduce consumption as costs increase. While these data demonstrate that reduced D2R signaling decreases appetitive motivation in response to costs, the question is whether this arises from decreased reinforcement efficacy of food reward or diminished willingness to expend energy in appetitive pursuit. The sucrose preference and two-bottle conditioning tests with the selective knockouts demonstrate that the hedonic value of sucrose and its efficacy in reinforcing learned associations is unchanged, arguing against a loss of reinforcement effi-

cacy, consistent with prior studies of haloperidol by Salamone et al. (1993).

These studies suggest that D2R expressed on iMSNs regulate behavioral thrift; that is, how much energy and effort an animal is willing to expend in the pursuit of reward. We propose a simple model by which the level of D2R expression on iMSNs gates the extent to which dopamine can inhibit the indirect pathway and relieve inhibition on cortical activity, regulating an inhibitory tone that must be overcome to initiate and sustain action. In response to dopamine release, reduced D2R disinhibits inhibitory tone on cortical activity to a lesser extent, increasing the activity required to overcome that inhibition; for example, requiring greater facilitation via direct pathway activation. In effect, this requires greater incentive motivation to overcome this gate and expend energy in pursuit of reward, which effectively increases the value of energy expended in work relative to the reward. We propose that striatal D2R determines how much value is required to initiate and sustain work; alternatively stated, D2R

gates the value of the energy expended in work (Beeler and Mourra, 2018).

Role of learning, synaptic plasticity and reinforcement

D2R regulates both synaptic plasticity (Kreitzer and Malenka, 2008; Shen et al., 2008; Lovinger, 2010) and cell excitability in indirect pathway MSNs (Surmeier et al., 2007), modulating both learning and on-going neurotransmission. As D2R modulates both indirect pathway inhibition and corticostriatal plasticity, both presumably contribute to the decreased willingness to expend energy in the pursuit of food observed here. While considerable evidence suggests that dopamine can modulate behavioral response to costs, as demonstrated here, a recent study has demonstrated that costs modulate dopamine signals that arise from and mediate learning (Tanaka et al., 2019). Specifically, dopamine signals in response to both cues that predict reward and in response to received reward are greater when the costs associated with those stimuli are greater. This could potentially describe a mechanism by which escalating costs facilitate learning that effectively increases the value of reward (see also Kacelnik and Marsh, 2002) and facilitates the increased effort necessary to obtain that reward, as observed here in wild-type. That is, while dopamine can

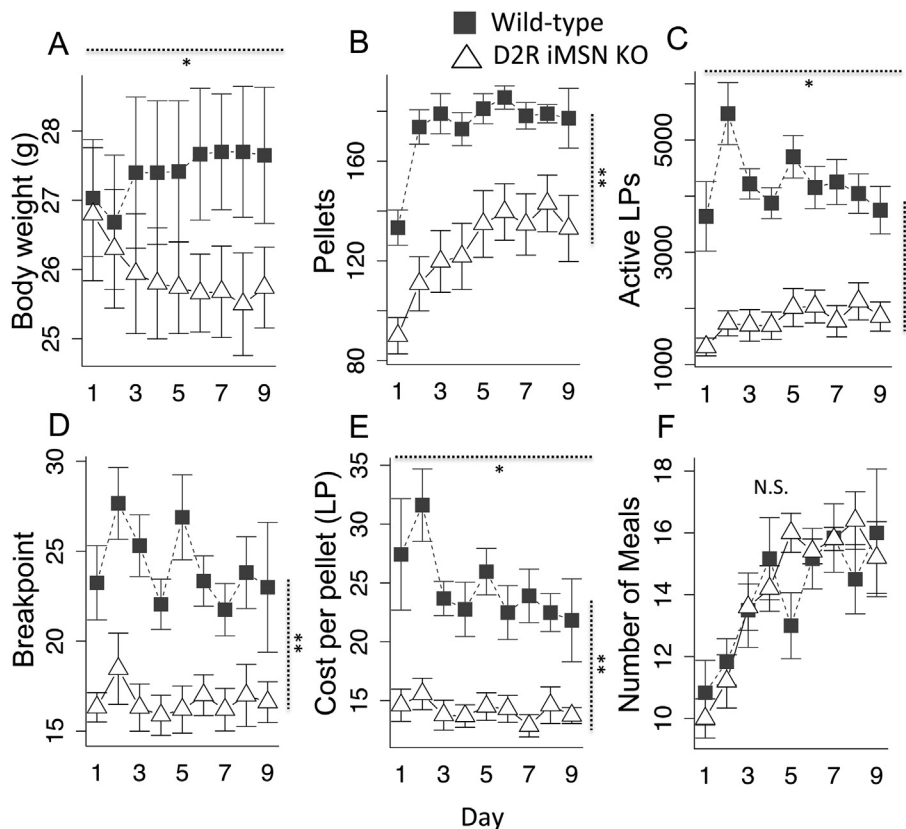


Fig. 5. D2R iMSN KO in homecage progressive ratio. (A) Daily body weight (B) daily consumption, (C) daily lever presses, (D) daily breakpoint, (E) daily average cost per pellet, (F) daily total number of meals. Vertical dotted lines indicate genotype main effect statistic, horizontal dotted lines indicate genotype × day statistic. $N = 5$, * $p < .05$, ** $p < .01$, *** $p < .001$. Error bars, S.E.M.

modulate effort, i.e., signal the value of work (Hamid et al., 2015), the Tanaka et al (2019) study suggest that learning can scale that dopamine-signaled value to adapt to environmental conditions and contingencies, suggesting one way in which dopamine modulation of MSN excitability and corticostriatal plasticity—current and future behavior—may be integrated to achieve adaptation in response to an environmental economy.

Our study and those of Wise and colleagues (e.g., Wise et al., 1978) are in agreement in that we both show that D2 blockade substantially reduces effort to obtain reward. Our studies differ in that Wise et al (1978) observed a gradual decrease across sessions consistent with learning, i.e., extinction mimicry, while we did not observe a gradual decrease but an adjustment in behavioral strategy that reduced costs but maintained consumption/reward. We suggest the different paradigms (session-based vs. homecage) capture different aspects of the same D2R-related phenomenon. The session-based experiments of Wise and colleagues breaks experience and learning into discrete blocks (sessions) distributed across time that allows observation of incremental changes as experience accrues, but does not provide insight into how these changes affect adaptive behavior in a naturalistic foraging environment. Our closed-economy, homecage paradigm precludes this block-by-block observation of experience and learning

as a 24 h period collapses the equivalent of 32 45-min sessions time-wise into a single data point. However, our paradigm allows observation of how the effects of haloperidol alter self-regulated, adaptive foraging-like behavior, demonstrating no change in appetitive motivation or reduction in consumption, only an increase in the energetic efficiency in food pursuit.

It is interesting that faced with escalating costs, the selective knockouts, unlike the mice administered haloperidol, do not compensate for smaller meals with increased meal frequency. The deletion of D2R in iMSNs likely impairs or even inverts corticostriatal plasticity (Calabresi et al., 1997). LTD in corticostriatal synapses onto the indirect pathway can allow learning to selectively disinhibit specific stimuli and responses. In the haloperidol studies, because of the continuous nature of the homecage paradigm, blockade of disinhibitory learning is not complete, i.e., as the drug is metabolized, continued pressing and reward can reinstate prior learning. In the knockouts, the loss of D2R is absolute and imposes an inflexible, non-selective inhibitory gate that operates independently

of dopamine, modulating both iMSN excitability and synaptic plasticity. If dopamine signals ‘the value of work’ (Hamid et al., 2015), iMSNs without D2R don’t get the message, or rather they overvalue the energy required for work relative to the value of the reward.

Does reduced D2R drive overconsumption in obesity?

A prominent theory proposes that D2R is reduced in obesity, which generates compulsive overeating, borrowing the reward deficiency hypothesis from the addiction literature (Blum et al., 2014). Whether D2R is reduced in obesity is increasingly contested as more studies emerge (Hardman et al., 2014). Nevertheless, the data reported here suggest that reduced D2R signaling does not increase appetitive motivation nor induce compulsive over-consumption. On the contrary, if pursuit of food requires effort, reduced D2R decreases willingness to exert effort in the service of food motivation, even when hunger is increased, as in the scarcity paradigm. Our findings are consistent with a rich literature dating back decades from Wise (review, Wise, 2004), Salamone (review, Salamone et al., 2007) and others showing that reduced dopamine or D2R blockade decreases appetitive motivation. More recently, two studies using mouse genetics to reduce D2R have demonstrated that D2R

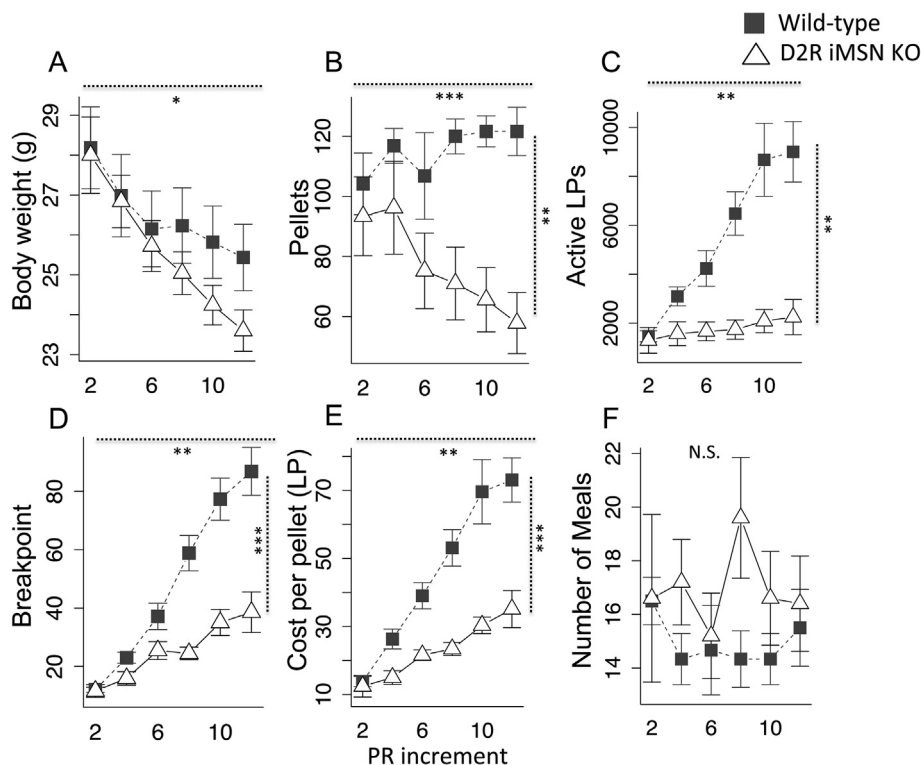


Fig. 6. D2R iMSN KO in escalating homecage progressive ratio (scarcity). (A) Daily body weights, (B) daily consumption, (C) daily lever presses, (D) daily breakpoint, (E) daily average cost per pellet, (F) daily total number of meals. Vertical dotted lines indicate genotype main effect statistic, horizontal dotted lines indicate genotype $\times$ day statistic. $N = 5$, $*p < .05$, $**p < .01$, $***p < .001$. Error bars, S.E.M.

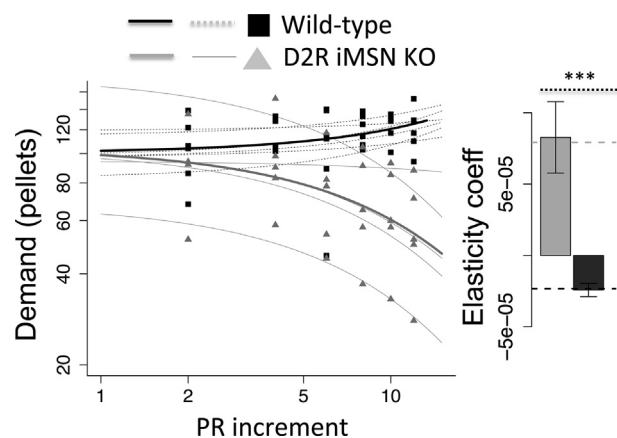


Fig. 7. Exponential demand curve fit to D2R iMSN KO and wild-type littermate controls. Data were fit for each individual mouse to exponential demand model (methods), yielding a best fit alpha parameter that describes elasticity. Actual data plotted as points (gray triangles, KOs; black squares, WT) with thin traces displaying fits for individual mice (gray, KOs; black, WT). Bold lines show best fits to genotype group data. The elasticity coefficient (alpha) for individual fits were averaged by genotype, shown in bar graph to right. $N = 5$, $***p < .001$. Error bars, S.E.M.

reduction does not increase consumption, even under palatable, high fat, dietary induced obesity conditions; instead, activity is dramatically reduced across multiple measures, including voluntary wheel-running, homecage

activity and open field activity (Beeler et al., 2016; Friend et al., 2016). The one study, to our knowledge, that putatively runs counter to this is from Johnson and Kenny (2010) where the authors knockdown D2R in rats using lentivirus and show that the rats are less affected by aversive stimuli in pursuit of food reward. However, there was no difference between the knockdowns and controls in bodyweight or consumption (Johnson and Kenny, 2010, Fig. 6C, D).

None of the theorizing about reduced D2R driving compulsive consumption takes into account the role of D2R in regulating activity and behavioral energy expenditure. The work reported here, as well as other recent mouse genetic studies (Beeler et al., 2016; Friend et al., 2016), suggest that the effect of D2R likely lies more in reducing willingness to expend energy in voluntary activity than in driving compulsive appetitive motivation. Activity levels are reduced in obesity (Friend et al., 2016). Putative obe-

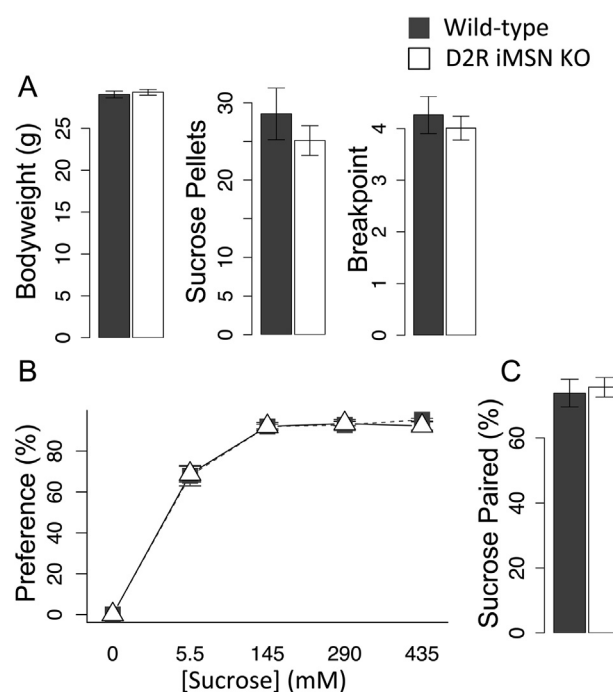


Fig. 8. Sucrose preference and reinforcement in D2R iMSN KO mice. (A) Concurrent choice: body weight, sucrose pellets earned and breakpoint, $N = 5$, (B) homecage sucrose preference, $N = 11/13$ (WT/KO) (C) Two-bottle conditioning, percent preference for bottle previously paired with sucrose in choice test with water in both bottles, $N = 10/12$ (WT/KO). Error bars, S.E.M.

sity related reductions in D2R may gate behavioral activation and decrease physical activity, making it difficult to sustain voluntary exercise regimens important both for health and maintaining weight loss (Levin and Dunn-Meynell, 2004; MacLean et al., 2009, 2015; DeLany et al., 2014). These data suggest that studies of D2R in obesity, in both human and animal subjects, should assess physical activity and voluntary exercise.

Limitations and caveats

Both haloperidol and selective genetic deletion of D2R do not isolate D2R in the dorsal versus ventral striatum. Recent studies have suggested that D2R may be differently affected in these regions in obesity and may, therefore, contribute differently (Guo et al., 2014), though our studies indicate the *net* effect when D2R is deleted in both regions. The genetic deletion is constitutive, thus potential developmental effects could come into play. However, there are no indications of gross abnormalities in the mutant mice and a similar phenotype between the pharmacological and selective genetic manipulation strengthen the argument that observed behavioral alterations arise from altered D2R. The haloperidol results argue against developmental causes in knockouts while D2R selectivity in the knockouts argue against non-specific effects in haloperidol. Finally, both haloperidol and selective deletion of D2R can impair motor learning (Beeler et al., 2016); however, we see no evidence of impaired learning in acquisition of lever pressing. Within the scarcity paradigm, the D2R iMSN KOs increase their lever pressing as costs increase; each increase indicates they were capable of pressing more at the prior cost but, effectively, chose not to. This is mirrored in the open field where their reduced activity arises from fewer ambulatory episodes (fewer initiations), shorter episodes (earlier termination of locomotion) and greater time resting but no difference in velocity of movement, again indicating a motivational rather than motor impairment.

D2R has been implicated in numerous behavioral functions, including the regulation of appetitive motivation, voluntary activity/behavioral energy expenditure, behavioral flexibility and learning. Our thrift hypothesis posits dopamine as a primary substrate regulating allocation of resources, with D2R serving as a gate for energy (resource) expenditure—or ‘cost controller’ (Beeler and Mourra, 2018). The studies reported here are consistent with striatal D2R gating behavioral energy expenditure and regulating cost-sensitivity in decision-making.

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