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Journal Item

OXFORD

International Journal of Neuropsychopharmacology, 2015, 1–11

doi:10.1093/ijnp/pyu017
Research Article

RESEARCH ARTICLE

Bupropion Increases Selection of High Effort Activity in Rats Tested on a Progressive Ratio/Chow Feeding Choice Procedure: Implications for Treatment of Effort-Related Motivational Symptoms

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Abstract

Background: Depression and related disorders are characterized by deficits in behavioral activation, exertion of effort, and other psychomotor/motivational dysfunctions. Depressed patients show alterations in effort-related decision making and a bias towards selection of low effort activities. It has been suggested that animal tests of effort-related decision making could be useful as models of motivational dysfunctions seen in psychopathology.

Methods: Because clinical studies have suggested that inhibition of catecholamine uptake may be a useful strategy for treatment of effort-related motivational symptoms, the present research assessed the ability of bupropion to increase work output in rats responding on a test of effort-related decision-making (ie, a progressive ratio/chow feeding choice task). With this task, rats can choose between working for a preferred food (high-carbohydrate pellets) by lever pressing on a progressive ratio schedule vs obtaining a less preferred laboratory chow that is freely available in the chamber.

Results: Bupropion (10.0–40.0 mg/kg intraperitoneal) significantly increased all measures of progressive ratio lever pressing, but decreased chow intake. These effects were greatest in animals with low baseline levels of work output on the progressive ratio schedule. Because accumbens dopamine is implicated in effort-related processes, the effects of bupropion on markers of accumbens dopamine transmission were examined. Bupropion elevated extracellular dopamine levels in accumbens core as measured by microdialysis and increased phosphorylated dopamine and cyclic-AMP related phosphoprotein 32 kDaltons (pDARPP-32) immunoreactivity in a manner consistent with D1 and D2 receptor stimulation.

Conclusion: The ability of bupropion to increase exertion of effort in instrumental behavior may have implications for the pathophysiology and treatment of effort-related motivational symptoms in humans.

Keywords: dopamine; nucleus accumbens; depression; fatigue; animal models

Received: Apirl 03, 2014; **Revised:** May 23, 2014; **Accepted:** May 28, 2014

Introduction

Depression is marked by various emotional and cognitive symptoms but is also characterized by effort-related motivational and psychomotor symptoms, including psychomotor retardation, anergia, lassitude, and fatigue (Stahl 2002; Caligiuri et al., 2003; Demyttenaere et al., 2005; Treadway and Zald 2011; Fava et al., 2013). The severity of effort-related symptoms in depression is correlated with problems with employment, social function, and treatment outcomes (Tylee et al., 1999; Stahl 2002), and these motivational symptoms are highly resistant to treatment in many people (Stahl 2002; Fava et al., 2013). Moreover, recent papers emphasize that many people with major depression have fundamental deficits in exertion of effort in reward seeking that do not depend simply upon problems with experiencing pleasure in response to a primary motivational stimulus (Treadway and Zald, 2011; Treadway et al., 2012a; Argyropoulos and Nutt, 2013). The neural basis of the effort-related dysfunctions in depression is still being characterized, but evidence implicates central dopamine (DA), striatal areas, and cortical mechanisms (Hickie et al., 1999; Caligiuri and Ellwanger et al., 2000; Schmidt et al., 2001; Volkow et al., 2001; Salamone et al., 2006, 2007; Tellez et al., 2008; Treadway and Zald, 2011). Moreover, effort-related motivational symptoms appear to be some of the most common psychiatric symptoms observed in general medicine (Demyttenaere et al., 2005) and are seen in multiple disorders, including schizophrenia, Parkinsonism, and multiple sclerosis (Friedman et al., 2007; Tellez et al., 2008; Gold et al., 2013). Because of the clinical significance of these activational or effort-related motivational symptoms and the growing emphasis on identifying neural circuits related to specific psychiatric symptoms (ie, the Research Domain Criterion approach), it is critical to develop animal models that assess effort-related processes.

It has been suggested that animal tests of effort-related decision-making could be useful for modeling motivational dysfunctions seen in psychopathology (Salamone et al., 2006, 2007; Salamone and Correa, 2012). Effort-based decision-making is studied with tasks offering choices between high-effort options leading to highly valued reinforcers vs low-effort/low-reward choices. With animals, such tasks include a T-maze barrier climbing task (Salamone et al., 1994; Cousins et al., 1996; Hauber and Sommer 2009; Mott et al., 2009; Pardo et al., 2012; Mai et al., 2012), effort discounting (Floresco et al., 2008; Bardgett et al., 2009), and operant procedures offering choices between responding on ratio schedules for preferred reinforcers vs approaching and consuming less preferred ones (Salamone et al., 1991, 2002; Schweimer and Hauber 2005; Randall et al., 2012). Research has highlighted the effort-related functions of DA systems, particularly accumbens DA. Across multiple tasks, low doses of DA antagonists and accumbens DA depletions or antagonism shift choice behavior, decreasing selection of high-effort/high-reward options and increasing selection of low-effort/low-reward choices (Salamone et al., 1994, 2007; Nowend et al., 2001; Mai et al., 2012; Pardo et al., 2012). Moreover, these effects of dopaminergic manipulations are not due to reinforcer devaluation or suppression of primary food motivation or appetite (Salamone et al., 1991, 2002; Koch et al. 2000; Sink et al., 2008; Randall et al., 2012; Nunes et al., 2013b). Recent studies have shown that reduced selection of high-effort activities in rats is induced by manipulations associated with depression, including muscarinic receptor stimulation (Nunes et al., 2013a; see also Janowski et al. 1994; Chau et al. 2001; Rada et al. 2006 for discussion of acetylcholine and depression), stress (Shafiei et al., 2012), injections of the proinflammatory cytokine interleukin-1β (Nunes et al., 2014), and administration of the catecholamine-depleting agent tetrabenazine (Nunes et al., 2013b). These observations are consistent with recent clinical data demonstrating that people with major depression show a reduced likelihood of selecting high-effort alternatives when assessed in human tests of effort-related choice (Treadway et al., 2012a).

Animal models of effort-based choice are also useful for the assessment of drug treatment strategies, and recent studies have investigated the effects of muscarinic acetylcholine and adenosine A_{2A} receptor antagonists (Nunes et al., 2013a, 2013b, 2014) for their ability to reverse effort-related impairments. Another compound that has been assessed is the antidepressant bupropion, which is a drug that can inhibit catecholamine uptake and facilitate vesicular uptake of DA (Dwoskin et al., 2006). Bupropion has been shown to reverse the effects of tetrabenazine on effort-related choice behavior in rats tested on the T-maze barrier choice task (Yohn et al., in press), the concurrent fixed ratio 5/chow feeding choice task (Nunes et al., 2013b), and the concurrent progressive ratio (PROG)/chow feeding choice task (Randall et al., 2014). The evaluation of catecholamine uptake inhibitors on tests of effort-related function is important because of clinical research indicating that catecholamine uptake blockade can be a relatively effective strategy for the treatment of psychomotor/motivational symptoms (Rampello et al., 1991; Stahl, 2002; Demyttenaere et al., 2005; Papakostas et al., 2006; Pae et al., 2007; Fava et al., 2013). Thus, the present studies evaluated the ability of bupropion to enhance responding on a PROG/chow feeding choice task. There are several variants of this task (Schweimer and Hauber, 2005; Beeler et al., 2012), and the specific procedure used was one that has previously been employed to assess drug effects in our laboratory (Randall et al., 2012, 2014). This specific procedure was chosen, because the PROG schedule gradually increases the lever-pressing requirement and therefore presents the animal with a gradually incrementing work-related cost. In addition, this procedure generates enormous individual differences in performance (Randall et al., 2012, 2014), which allows for the differential assessment of drug effects in high vs low performers. Because of the literature implicating accumbens DA in effort-related processes (Salamone et al., 1997, 2003, 2007; Salamone and Correa 2012; Nunes et al., 2013a, 2013b), including performance on the PROG/chow feeding choice task (Randall et al., 2012, 2014), the effects of bupropion on pre- and postsynaptic markers of accumbens DA transmission also were examined (ie, microdialysis to measure extracellular DA and phosphorylated dopamine and cyclic-AMP related phosphoprotein 32 kDaltons (pDARPP-32) immunoreactivity as a marker of DA-related signal transduction).

Methods

Animals

Seventy-two adult male Sprague-Dawley rats were housed in a colony at 23°C with 12-h–light/–dark cycles (lights on at 7:000 am). Rats in experiment 1 (n = 42) weighed 300 to 350 g at the beginning of the study and were initially food restricted to 85% of their free-feeding body weight for training; they were fed supplemental chow to maintain weight throughout the study, with water available ad libitum in home cages, and were allowed modest weight gain throughout the experiment. All other rats (n = 30) weighed 300 to 350 g at the beginning of the study and had ad libitum access to laboratory chow and water in home cages. Animal protocols were approved by the University of

Connecticut Institutional Animal Care and Use Committee and followed NIH guidelines (DHEW Publications, NIH, 80-23).

Pharmacological Agents and Dose Selection

Bupropion hydrochloride (Alfa Aesar, Ward Hill, MA) was dissolved in 0.9% saline solution that also served as the vehicle control. Doses were selected based on previous papers (Bruijnzeel and Markou, 2003; Nunes et al., 2013b).

Behavioral Procedures

Behavioral sessions were conducted in operant chambers ($28 \times 23 \times 23\,cm^3$; Med Associates, Putney, VT) with 30-minute sessions 5 d/wk. Rats were initially trained to lever press on a continuous reinforcement schedule (high-carbohydrate 45-mg pellets, Bio-serv, Frenchtown, NJ) and then shifted to the PROG schedule (Randall et al., 2012). For PROG sessions, the ratio started at fixed ratio (FR)1 and was increased by 1 additional response every time 15 reinforcements were obtained (FR1 × 15, FR2 × 15, etc.). A "time-out" feature deactivated the response lever if 2 minutes elapsed without a completed ratio. After 9 to 10 weeks of PROG training, chow was introduced. Weighed amounts of laboratory chow (Laboratory Diet, 5P00 Prolab RMH 3000, Purina Mills, St. Louis, MO; typically 15–20 g) were concurrently available on the floor of the chamber during the PROG sessions. Chow intake was determined by weighing the remaining food (including spillage). Rats were trained on the PROG/chow feeding choice procedure for 4 to 5 weeks, after which drug testing began. On baseline and drug treatment days, rats consumed all the operant pellets that were delivered during each session.

Microdialysis and High-Performance Liquid Chromatography

Rats were anesthetized with a 1.0-mL/kg intraperitoneal (IP) injection of a solution containing 10.0 mL of 100 mg/mL ketamine plus 0.75 mL of 20.0 mg/mL xylazine (Phoenix Scientific, Inc., St. Joseph, MO). While in the stereotax (Kopf, Tujunga, CA; incisor bar 5.0 mm above interaural line), rats received unilateral implantations of a 10.0-mm probe guide cannula (Bioanalytical Systems, Indianapolis, IN). The tips of the guide cannulae were implanted 2.0 mm above accumbens core (anterior/posterior: +2.8 mm, medial/lateral: ±1.4 mm, dorsal/ventral: −5.8 mm from bregma; counterbalanced left vs right) and secured to the skull with stainless steel screws and cement. Stainless steel stylets were inserted into the guide cannulae to maintain patency. Animals were housed in separate cages and allowed 7 days postsurgical recovery.

Rats with implanted cannulae were habituated in Plexiglas chambers ($28 \times 28 \times 23\,cm^3$) the day before sampling for 8 hours with infusion pumps running. The following day, probes were inserted through the cannula, and artificial cerebrospinal fluid was pumped through at a rate of 2 µL/min (syringe pump, Harvard Apparatus, Cambridge, MA). Two hours postinsertion, sampling began and continued for 6 hours. After sampling, the probe was removed, and after euthanasia, histological analyses were performed to verify placements. Samples were frozen and analyzed for DA content using reverse-phase high-performance liquid chromatography with electrochemical detection (ESA, New Bedford, MA; Segovia et al., 2011; Nunes et al. 2013b). Each liter of mobile phase contained 27.6 g sodium phosphate monobasic monohydrate, 8% methanol, 750 µL 0.1 M ethylenediaminetetraacetic acid, and 2000 µL 0.4 M sodium octyl sulfate dissolved in dH_2O (pH = 4.5). DA standards were assayed before, during, and after the dialysis samples.

Immunocytochemistry for Phosphorylated DA and c-AMP Related Phophoprotein-32 kDaltons (pDARPP-32)

Two hours after injection, rats were perfused with 3.7% formaldehyde and brains were extracted. Tissue was fixed in 3.7% formaldehyde overnight and moved to 30% sucrose cryo-protectant. Then 50-µm sections were cut using a cryostat. Tissue was washed in phosphate buffered saline (PBS) and bathed in blocking solution (0.1% Triton-X, 5.0% normal donkey serum, PBS) on a rotating shaker for 60 minutes, then washed for 15 minutes in PBS, and incubated in primary antibody (donkey anti-rabbit Thr34, donkey anti-rabbit Thr75, 1:500, Santa Cruz Bioscience, CA) with 0.1% Triton-X, 5.0% normal donkey serum, PBS, on a refrigerated rotating shaker for 24 hours. Next, tissue was washed for 15 minutes in PBS and incubated in secondary antibody (Alexaflour anti-rabbit 488 for pDARPP-32(Thr34) and pDARPP-32(Thr75), 1:200, Life Scientific) with 0.1% Triton-X, 5.0% normal donkey serum, PBS, on a rotating shaker for 120 minutes. Tissue was then washed for 15 minutes in PBS, wet mounted on slides, and dried overnight. Tissue was imaged on an Axio Imager-M2 fluorescence microscope. Images used for counting cells were 20× magnification. Cells were counted using a custom macro for ImageJ.

Experiment 1: The Effects of Bupropion on PROG/Chow Performance

Rats (n = 42) were trained as described above and were run on the PROG/chow feeding choice procedure 5 d/wk. On drug test days, they received IP injections of either saline vehicle or 10.0, 20.0, or 40.0 mg/kg bupropion, 30 minutes before testing, using within-subjects design with each subject receiving all drug treatments, once per week, in a random order. Baseline training days were conducted on the other 4 days each week.

Experiment 2: Effects of Bupropion on nucleus accumbens Core DA in Untrained Rats as Measured by in-Vivo Microdialysis

Rats were implanted with dialysis guide cannulae and had dialysis probes inserted on the morning of the drug test as described above. On test days, rats (n = 5/group) received injections of 20.0 or 40.0 mg/kg bupropion or vehicle following the second baseline sample, and 6 additional dialysis samples were collected.

Experiment 3: Effects of Bupropion on NAc and Neostriatal DA Signaling in Untrained Rats as Measured by pDARPP-32 Immunoreactivity

Rats (n = 5/group) received IP injections of saline vehicle or 20.0 or 40.0 mg/kg bupropion 2 hours before perfusion for tissue analysis.

Statistical Analyses

Animals in experiment 1 were separated into high- and low-performance groups by a median split, and total lever presses, highest ratio achieved, active lever time, and chow consumption on the PROG/chow were analyzed with a 2 (performance group) × 4 (drug treatment) factorial analysis of variance (ANOVA) with repeated measures on the drug treatment

factor. Based on the performance group × treatment interactions for all 4 behavioral variables analyzed, separate ANOVAs and nonorthogonal planned comparisons (Keppel, 1991) of each performance group were used to determine differences between each drug treatment vs vehicle. Previous research has shown that there is considerable variability in performance of the PROG/chow choice task (Randall et al., 2012), and the present work as well as recent studies indicate that baseline performance is a stable characteristic across many weeks of training (data not shown). Additionally, total lever presses under each drug treatment condition were analyzed between high and low performers using analysis of simple effects, and effect sizes (partial ε^2) for each variable and performance group across all doses were calculated to determine the magnitude of the drug treatment effects across each variable and group. For the microdialysis experiment, DA levels were analyzed as percentage change from baseline, with the mean of the 2 samples immediately preceding the lever-pressing session serving as the 100% baseline level. Animals that had a variability of >35% from the mean during the 2 baseline samples were excluded from further analyses (2 animals were excluded that failed to meet this criterion). Factorial ANOVA with repeated measures on the time factor was used to analyze the DA data. In experiment 3, mean number of pDARPP-32(Thr34) and pDARPP-32(Thr34) positive cells across each region of interest were analyzed using simple ANOVA with posthoc analysis (Tukey) to determine differences between treatment levels.

Results

Experiment 1: Bupropion Increases PROG/Chow Responding

Rats were split into 2 performance groups (high vs low) using a median split of total lever presses under the vehicle condition and analyzed with ANOVA. There were significant performance group × drug treatment interactions for all 4 variables (total lever presses: $F[3,120]=2.726$, $P<.05$), highest ratio achieved ($F[3,120]=7.201$, $P<.05$), active lever time ($F[3,120]=7.038$, $P<.05$), and chow consumption ($F[3,120]=7.904$, $P<.05$). Based on these findings, high performers and low performers were separately analyzed with repeated-measures ANOVA to characterize performance in each group. There was a significant effect of treatment in high performers on total lever presses ($F[3,60]=9.468$, $P<.05$), highest ratio achieved ($F[3,60]=7.015$, $P<.05$), active lever time ($F[3,60]=12.366$, $P<.05$), and chow consumption ($F[3,60]=66.461$, $P<.05$). Planned comparisons demonstrated that total lever presses, highest ratio achieved, and active lever time were all increased at 20.0 and 40.0 mg/kg bupropion compared with vehicle ($P<.05$). Furthermore, chow consumption was decreased in high performers at all doses compared with vehicle ($P<.05$). For low performers, there also were significant effects of treatment in low performers on total lever presses ($F[3,60]=40.359$, $P<.05$), highest ratio achieved ($F[3,60]=46.128$, $P<.05$), active lever time ($F[3,60]=63.096$, $P<0.05$), and chow consumption ($F[3,60]=160.489$, $P<.05$). The highest ratio achieved and active lever time in low performers were both significantly increased at 20.0 and 40.0 mg/kg bupropion compared with vehicle ($P<.05$; planned comparisons), whereas total lever presses were increased only at 40.0 mg/kg compared with vehicle ($P<.05$). Furthermore, chow consumption in low performers was decreased at all doses of bupropion compared with vehicle ($P<.05$).

To further analyze differences between performance groups on each measure, individual drug treatment levels were analyzed. For lever pressing, ANOVA revealed that low performers responded less than high performers on vehicle ($F[1,40]=15.822$, $P<.05$), 10.0 mg/kg ($F[1,40]=22.796$, $P<.05$), and 20.0 mg/kg ($F[1,40]=33.295$, $P<.05$) but did not differ from high performers at 40.0 mg/kg ($F[1,40]=1.449$, not significant). Similarly, for highest ratio achieved for low performers reached a lower ratio than high performers on vehicle ($F[1,40]=27.644$, $P<.05$), 10.0 mg/kg ($F[1,40]=36.370$, $P<.05$), and 20.0 mg/kg ($F[1,40]=39.729$, $P<.05$) but were not different from high performers at 40.0 mg/kg bupropion ($F[1,40]=0.274$, n.s.). Moreover, low performers showed less active lever time compared with high performers on vehicle ($F[1,40]=18.068$, $P<.05$), 10.0 mg/kg ($F[1,40]=16.628$, $P<.05$), and 20.0 mg/kg ($F[1,40]=25.698$, $P<.05$) but not at 40.0 mg/kg bupropion ($F[1,40]=0.002$, n.s.). Finally, with chow intake, low performers consumed significantly more chow compared with high performers on vehicle ($F[1,40]=25.160$, $P<.05$), 10.0 mg/kg ($F[1,40]=19.637$, $P<.05$), and 20.0 mg/kg ($F[1,40]=30.121$, $P<.05$) but not at 40.0 mg/kg bupropion ($F[1,40]=0.162$, n.s.). Moreover, these performance group differences in the effects of bupropion were supported by measures of effect size (partial ε^2), in which low performers showed a greater effect of bupropion on total lever presses, highest ratio achieved, active lever time, and chow consumption compared with high performers (Table 1).

Experiment 2: Bupropion Increases Extracellular DA in NAc Core in Untrained Animals

The results of the microdialysis study are shown in Figure 2. Factorial ANOVA with repeated measures on the sample factor demonstrated that there was a significant overall difference across samples ($F[7,77]=12.815$, $P<.001$) and a significant overall difference across treatment groups (ie, the different groups of rats receiving vehicle, 20.0 or 40.0 mg/kg; $F[2,11]=7.978$, $P<.01$). Moreover, there was a significant sample × treatment interaction (ie, across the different dialysis samples and treatment groups; $F[14,77]=6.656$, $P<.001$). As a result of the significant interaction, each treatment group was separately analyzed with repeated-measures ANOVA. There was no difference across samples in vehicle-treated rats ($F[7,21]=1.561$, n.s.). However, there was a significant effect of treatment in both 20.0 mg/kg ($F[7,28]=7.669$, $P<.05$) and 40.0 mg/kg treated rats ($F[7,28]=10.657$, $P<.05$). Planned comparisons revealed that the postdrug sample 2 was significantly different from baseline in rats treated with 20.0 mg/kg bupropion ($P<.05$) and that samples 2, 3, 4, and 5 were significantly different from baseline in rats treated with 40.0 mg/kg bupropion ($P<.05$).

Experiment 3: Bupropion Increases Phosphorylated DARPP-32 Expression at Both Thr34 and Thr75 Residues

Figures 3 to 5 depict the effects of bupropion treatment on expression of pDARPP-32(Thr34) and pDARPP-32(Thr75) in

Table 1. Effect Sizes (Partial ε^2): Low Performers Show Greater Effect of Bupropion on All Measures Compared with High Performers

	High Performers	Low Performers
Total lever presses	0.321	0.669
Highest ratio achieved	0.260	0.698
Active lever time	0.382	0.759
Chow consumption	0.769	0.889

accumbens core, accumbens shell, and overlying dorsal striatum (neostriatum). Bupropion increased signs of DA-related signal transduction at both D1 and D2 family receptors (Figures 3 and 4). ANOVA revealed a significant effect of drug treatment on pDARPP-32(Thr34) expression in accumbens core ($F[2,12]=22.093$, $P<.05$), shell ($F[2,12]=12.862$, $P<.05$), and dorsal striatum ($F[2,12]=39.989$, $P<.05$). Posthoc analysis (Tukey) revealed that pDARPP-32(Thr34) expression in the accumbens core was significantly increased at 20.0 and 40.0 mg/kg ($P<.05$) compared with vehicle. These doses did not significantly differ from each other. In the accumbens shell and dorsal striatum, only 40.0 mg/kg bupropion increased pDARPP-32(Thr34) expression over vehicle ($P<.05$). In addition, there was a significant effect of treatment on pDARPP-32(Thr75) expression in accumbens core ($F[2,12]=4.191$, $P<.05$), shell ($F[2,12]=4.343$, $P<.05$), and dorsal striatum ($F[2,12]=5.473$, $P<.05$). pDARPP-32(Thr75) expression in accumbens core, shell, and dorsal striatum was significantly increased by 40.0 mg/kg bupropion ($P<.05$).

Discussion

Bupropion is a catecholamine uptake inhibitor that has been used for many years as an antidepressant (Dwoskin et al., 2006). Traditional rodent tests, such as forced swim and tail suspension, are sensitive to the effects of bupropion (Yamada et al., 2004; Kitamura et al., 2010). Bupropion (Wellbutrin) is frequently prescribed, and in 2010 it was reported to be the most commonly prescribed antidepressant in the United States (Milea et al., 2010). Moreover, this drug is particularly interesting because of evidence indicating that inhibition of DA uptake may be relatively effective for treating anergia, fatigue, or psychomotor symptoms observed in many depressed patients (Rampello et al., 1991; Stahl, 2002; Demyttenaere et al., 2005; Papakostas et al., 2006; Pae et al., 2007). Bupropion is capable of reversing the effort-related impairments induced by the vesicular monoamine transporter (VMAT)-2 inhibitor and DA-depleting agent tetrabenazine in rats (Nunes et al., 2013b; Randall et al., 2014). In contrast, the current studies investigated the effects of bupropion administered on its own to assess its ability to alter effort-based choice as measured by the PROG/chow feeding choice procedure. Bupropion shifted choice behavior and increased the tendency to work for food reinforcement, as marked by increases in all measures of PROG lever pressing (total lever presses, highest ratio achieved, and active lever time) (Figure 1) while decreasing consumption of the concurrently available chow. These data are consistent with a previous study showing that bupropion could increase food-reinforced responding on a conventional PROG schedule (Bruijnzeel and Markou, 2003). Nevertheless, as previously described (Randall et al., 2012), the PROG/chow feeding choice procedure provides additional information compared with conventional schedules, because the animal is given an explicit choice between lever pressing for food reinforcement and intake of an alternative food source (chow) as opposed to the choice between responding and not responding. In addition, the specific version of the PROG/chow feeding choice procedure used generates enormous individual variability, which is related to differences in drug response and markers of DA-related signal transduction (Randall et al., 2012). In the present study, the effects of bupropion were greater in low performers than high performers on all 4 behavioral measures, as indicated by the larger effect sizes seen with the low performers (Table 1). Moreover, despite the substantial differences in baseline performance on all variables, after injection of 40.0 mg/kg bupropion, there were no significant differences between high and low performers on any behavioral measure, indicating that this dose of bupropion made the 2 performance

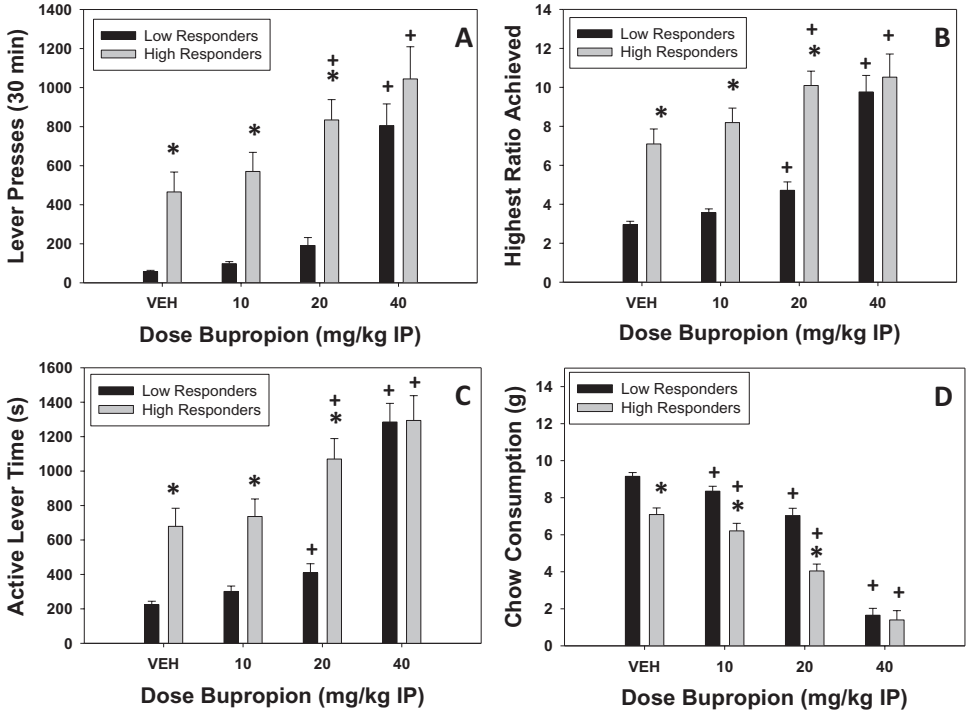

Figure 1. Effects of bupropion on progressive ratio (PROG)/chow performance in high and low responders. Mean (±SEM) number of total lever presses (A), highest ratio achieved (B), active lever time (in seconds; C), and chow consumption (in grams; D). (* $P<.05$, high responders different from low responders; + $P<.05$, bupropion different from vehicle in that specific performance group).

groups roughly equal. These findings demonstrate the utility of the PROG/chow feeding choice procedure as a model for assessing the effort-related effects of antidepressant drugs.

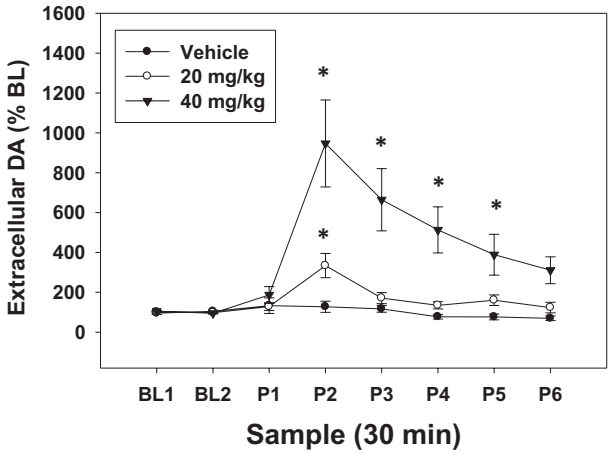

Figure 2. Bupropion increases extracellular dopamine (DA) in NAc core. Mean (±SEM) extracellular DA (expressed as percent baseline) in 30-minute samples. Two baseline samples were collected prior to injection of vehicle or bupropion. Six samples were collected following injection. (* $P < .05$, different from baseline).

To better understand the effects of bupropion on DA signaling, 2 different neurochemical measures were employed. Experiment 2 assessed the effects of bupropion on extracellular DA concentrations in accumbens core using microdialysis. Accumbens core was studied, because it is the DA terminal area in the striatal complex of rats that appears to be most consistently linked to the regulation of effort-related choice behavior (Cousins et al., 1993; Font et al., 2008; Mingote et al., 2008; Farrar et al., 2010; Ghods-Sharifi et al., 2010; Hauber and Sommer, 2010; Randall et al., 2012). Bupropion significantly increased accumbens extracellular DA at both 20.0 and 40.0 mg/kg, which were the behaviorally active doses in experiment 1. Furthermore, these increases were maximal during the same time span that an operant session would be taking place (30–60 minutes postinjection). The 20.0 dose of bupropion, which increased extracellular DA in nucleus accumbens by approximately 3-fold, significantly increased lever pressing in the high-performance group in experiment 1 but not the low-performance group. The 40.0-mg/kg dose of bupropion was needed to increase PROG lever pressing in the low-performance group, and the microdialysis study indicated that this dose produced a very large increase in extracellular DA (ie, 9- to 10-fold). These large increases in extracellular DA that were induced by the highest dose of bupropion are comparable with the increases seen with administration of other drugs that

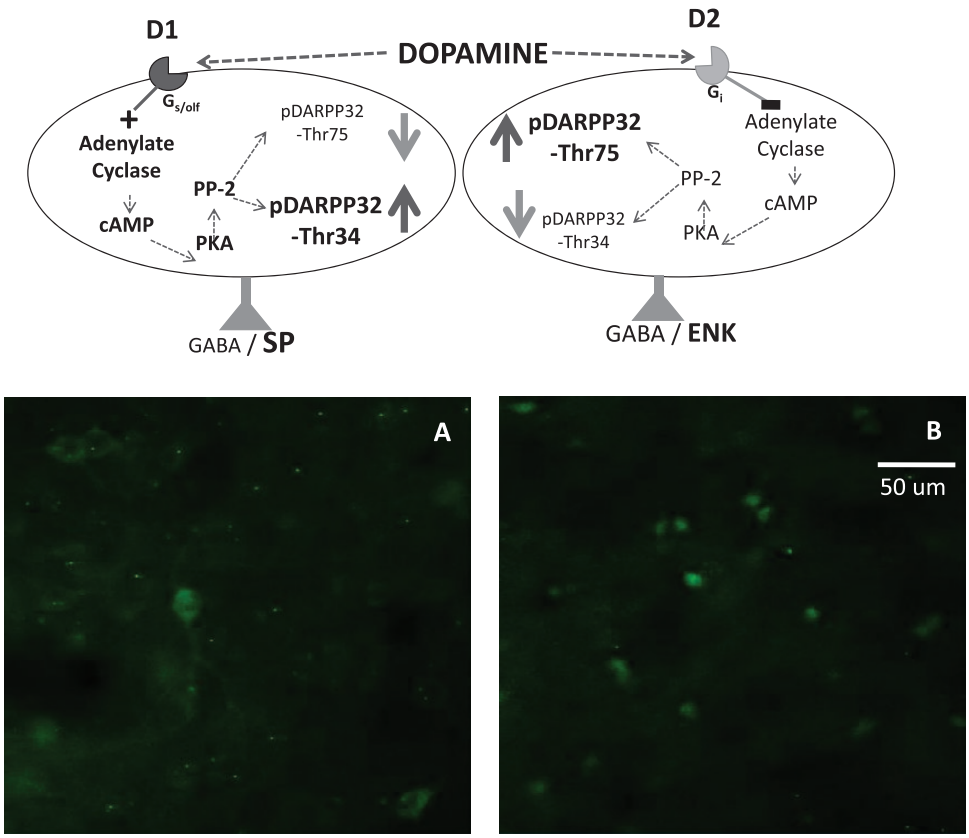

Figure 3. Top, DARPP-32 biochemistry in accumbens neurons containing dopamine (DA) D1 and D2 family receptors (see Bateup et al., 2008 for details). D1 receptor stimulation increases c-AMP production and protein kinase A (PKA) activity, which phosphorylates DARPP-32 to yield pDARPP-32(Thr34). D2 receptor stimulation decreases c-AMP production and protein kinase A activity, which decreases the dephosphorylation of pDARPP-32(Thr34) by protein phosphatase 2A (PP-2A), and therefore increases pDARPP-32(Thr75) expression. Bottom, High magnification photomicrographs of pDARPP-32(Thr34) (A) and pDARPP-32(Thr75) (B) staining in nucleus accumbens core, showing representative rats treated with 40.0 mg/kg bupropion. Images were taken at 40× magnification. Scale bar = 50 µm.

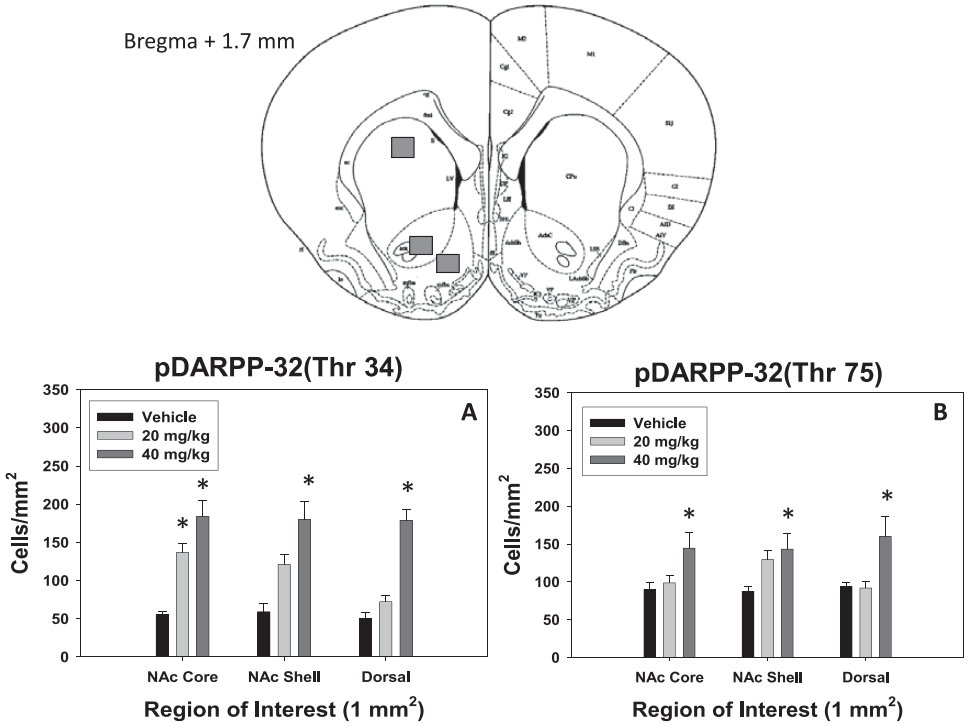

Figure 4. Top, Schematic diagrams of the relevant coronal section and specific brain regions depicted in bottom figures (based on the atlas of Paxinos and Watson, 1998). The squares indicate the placement of optical dissectors for counting pDARPP-32 positive cells. Bottom, Bupropion increases expression of pDARPP-32 at both Thr34 and Thr75 residues. A, Mean (±SEM) DARPP-32(Thr34) positive cells counted in each region of interest for each treatment group. B, Mean (±SEM) DARPP-32(Thr75) positive cells counted in each region of interest for each treatment group. (* $P < .05$, different from vehicle in each region of interest).

block DA uptake, including stimulants such as cocaine (Lenoir et al., 2007).

Experiment 3 assessed the effects of bupropion on accumbens and neostriatal pDARPP-32 immunoreactivity in untrained rats. The greatest effects were seen at 40.0 mg/kg, though pDARPP-32(Thr34) expression in the accumbens core was significantly increased at both 20.0 and 40.0 mg/kg, which was the same dose range as the behavioral effects observed in experiment 1. Both phosphorylated forms of DARPP-32 (ie, at the Thr34 and Thr75 amino acid residues) were responsive to bupropion treatment, although the magnitude of effects on pDARPP-32(Thr75) tended to be smaller than those seen with pDARPP-32(Thr34). Based on the microdialysis results showing increased extracellular DA after bupropion administration and on papers describing the role of DARPP-32 as a signaling protein (Svenningson et al., 2004; Bateup et al., 2008; Yger and Girault, 2011; Santerre et al., 2012; Segovia et al., 2012), it is likely that pDARPP-32(Thr34) increased after bupropion administration because of increased D1 receptor stimulation in substance P positive neurons, while pDARPP-32(Thr75) increased because of increased D2 receptor stimulation in enkephalin positive neurons (Figures 3 and 4). Thus, it appears that the doses of bupropion used in the present experiment increased DA transmission at multiple subtypes of medium spiny neurons (ie, those predominantly expressing D1 receptors and those expressing D2 receptors). However, double-labeling and tract-tracing methods would be necessary to confirm the efferent projection targets of these neurons.

Consistent with the hypothesis that bupropion is shifting choice behavior and increasing PROG lever pressing through actions on DA, previous studies have shown that interfering with DA transmission produces the opposite effect and decreases PROG lever pressing in rats responding on the PROG/chow feeding choice task. Administration of either D1 or D2 family antagonists, as well as the DA depleting agent tetrabenazine, all decrease PROG lever pressing in rats responding on the PROG/chow choice task (Randall et al., 2012, 2014). Although the effects of bupropion on preference between high-carbohydrate pellets and laboratory chow have not been studied, previous research has shown that other dopaminergic manipulations did not alter preference between the 2 different foods (Salamone et al., 1991; Nunes et al., 2013b). In addition, recent unpublished data from our laboratory indicate the high lever-pressing performance on the PROG/chow feeding choice task is not simply related to a higher degree of preference for high-carbohydrate food pellets relative to chow. Future research should also use choice tasks that involve selection of nonfeeding activities (eg, wheel running).

With increasing interest in the effort-related symptoms of depression (eg, Salamone et al., 2006; Treadway et al., 2011, 2012a), there is a growing need for treatments that effectively improve these symptoms. Bupropion can increase both DA and norepinephrine transmission (Hudson et al., 2012), but at this point, there is little evidence implicating norepinephrine in effort-related choice behavior, whereas considerable evidence supports a role for DA (Salamone et al., 2007; Salamone and Correa, 2012). Thus, the current findings showing that bupropion increases the tendency to work for food at doses that increase DA transmission are consistent with the suggested use of drugs that augment DA transmission as therapeutic treatments for effort-related motivational symptoms (Argyropoulos and Nutt, 2013; Soskin et al., 2013). As demonstrated here and in previous work (Nunes et al., 2013b; Randall et al., 2014), bupropion increases exertion of effort in otherwise untreated animals (experiment 1), and attenuates the effort-related deficits induced

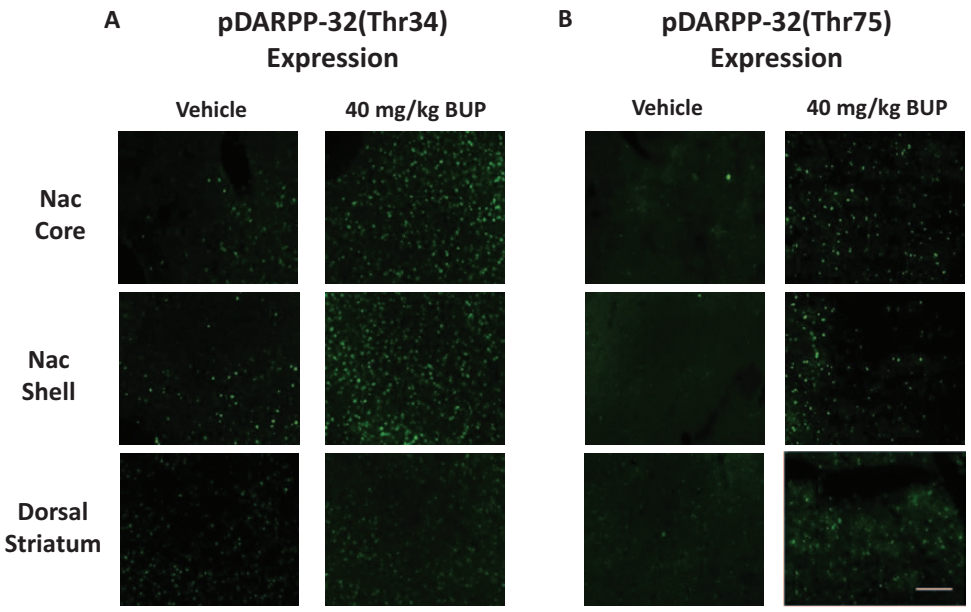

Figure 5. Photomicrographs of pDARPP-32(Thr34) (A) and pDARPP-32(Thr75) (B) staining in each region of interest, showing representative vehicle treated (left column) and rats treated with 40.0 mg/kg (right column).

by low doses of tetrabenazine that deplete accumbens DA and reduce DA-related signal transduction in rats. These findings are consistent with clinical studies reporting that patients treated with bupropion show improvements in effort-related motivational symptoms (Papakostas et al., 2006; Pae et al., 2007) and that clinically relevant doses of bupropion occupy DA transporters in vivo (Learned-Coughlin et al., 2003). Furthermore, in the current studies, bupropion increased lever pressing in low responders, bringing them up to the same level as high responders; this finding is particularly important in view of the recent report indicating that poor performers on this task show lower levels of DA-related signal transduction [ie, pDARPP-32(Thr34) expression] in accumbens core compared with high responders (Randall et al., 2012). Moreover, the present results are consistent with previous studies indicating that amphetamine increases exertion of cognitive effort in animals with low baseline performance (Cocker et al., 2012). Future research should assess a wider variety of drugs for their ability to enhance exertion of effort, including novel DA uptake inhibitors, monoamine oxidase inhibitors such as deprenyl (Randall et al., 2014), adenosine A_{2A} receptor antagonists (Randall et al., 2012; Nunes et al., 2013b, 2014), and drugs that inhibit norepinephrine and 5-HT uptake.

In summary, bupropion can increase the motivation to work for food reinforcement, particularly in animals with poor baseline performance. Together with studies using other behavioral procedures and drug treatments (Randall et al., 2012, 2014; Nunes et al., 2013a, 2013b), the present studies indicate that the PROG/chow feeding choice procedure is useful for the preclinical assessment of drug treatment of effort-related motivational symptoms in psychopathology. Moreover, bupropion exerts its behavioral effects in rats at doses that augment pre- and postsynaptic markers of DA transmission. These observations are consistent with the extensive body of evidence linking DA transmission to effort-related processes in animals (Salamone et al., 1994, 1997, 2003, 2007; Cagniard et al., 2006; Floresco et al., 2008; Mai et al., 2012; Salamone and Correa, 2012a; Nunes et al., 2013b; Trifilieff et al., 2013) and humans (Wardle et al., 2011; Treadway et al., 2012b) and with clinical studies indicating that DA transmission regulates effort-related motivational symptoms in depression and other disorders (Rampello et al., 1991; Brown and Gershon, 1993; Treadway and Zald, 2011; Argyropoulos and Nutt, 2013; Treadway and Pizzigali, 2014). Although motivational impairments are very common in depressed patients, they also are present across a wide spectrum of psychopathologies, including schizophrenia, Parkinsonism, multiple sclerosis, and immune system challenges (Salamone et al., 2006; Winograd-Gurvich et al., 2006; Dantzer et al., 2012; Gold et al., 2013; Markou et al., 2013; Nunes et al., 2014). Therefore, tests of effort-related choice behavior should not be viewed simply as animal models of depression per se. Instead, they are probably modeling a class of motivational symptoms that is characteristic of depression but also spans multiple disorders and conditions. This suggestion is consistent with the Research Domain Criteria approach, which places less emphasis on traditional diagnostic categories and instead focuses on the neural circuits mediating specific pathological symptoms (Cuthbert and Insel, 2013).

Acknowledgments

Many thanks to Hector Contreras for his help with conducting these experiments and to Regina Vontell, Nicole Segovia, Matthew Eastman, and Joanne Conover for assistance with the immunocytochemistry. This work was supported by a grant to J.D.S. from the National Institute of Mental Health (MH094966) and to M.C. from U. Jaume I (P1.1 A 2013-01) and UCONN SURF grants to M.R. and M.J.

Statement of Interest

J. Salamone has received grants from Pfizer, Roche, Shire, and Prexa.

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