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Pharmacological characterisation of the thermogenic effect of bupropion

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Abstract

The pharmacological mechanism of bupropion's thermogenic effect has been investigated in female Wistar rats by measuring oxygen consumption at thermoneutrality (29 °C). Bupropion (30 mg/kg) rapidly increased oxygen consumption (VO_2) with a maximum effect at 30 min, and VO_2 remained elevated throughout the 4-h experimental period. The nonselective 5-hydroxytryptamine (5-HT or serotonin) receptor antagonist, metergoline (1 mg/kg), and the α_1-adrenoceptor antagonist, prazosin (1 mg/kg), had no effect on the VO_2 response to bupropion, whereas the α_2-adrenoceptor antagonist, RS79948 [(8a*R*, 12*aS*, 13*aS*)-5,8,8*a*,9,10,11,12,12*a*,13,13*a*-decahydro-3-methoxy-12-(ethylsulphonyl)-6*H*-isoquino[2,1-*g*][1,6]-naphthyridine hydrochloride] (1 mg/kg), potentiated the response. The VO_2 response to bupropion during the first 60 min was significantly inhibited by a high dose of the nonselective β-adrenoceptor antagonist, propranolol (20 mg/kg), but it had no effect at a low dose (1 mg/kg). Pretreatment with the dopamine D2/D1 receptor antagonist, (+)butaclamol (200 μg/kg), caused a partial, but significant, inhibition ($P<0.01$) of the VO_2 response to bupropion during the first 60 min, and this antagonist abolished the effect of bupropion between 90 and 240 min. Pretreatment with a combination of a high dose of propranolol (20 mg/kg) and (+)butaclamol (200 μg/kg) prevented any increase in VO_2 induced by bupropion. It is concluded that the β_3-adrenoceptor subtype, as well as dopamine D2/D1 receptors, is responsible for the increase in oxygen consumption induced by bupropion. We have previously demonstrated that bupropion did not significantly reduce food intake in rats. Hence, in this species, its weight-reducing action predominantly results from thermogenesis mediated via activation of β_3-adrenergic and dopamine D2/D1 receptors. Because bupropion has also been reported not to alter food intake in the clinic, thermogenesis may also contribute to its antiobesity effect in man.

Keywords: Thermogenesis; Oxygen consumption; Bupropion; Brown adipose tissue; Brown fat

1. Introduction

Bupropion is a monoamine reuptake inhibitor that is approved for treatment of major depression and for smoking cessation (Ascher et al., 1995; Hughes, 2000). It has been shown that subjects receiving bupropion for the treatment of depression and smoking cessation gained significantly less weight than placebo-treated patients (Settle et al., 1999; Jorenby et al., 1999). Sustained weight loss in nondepressed obese subjects has also been recently reported in a double-blind, placebo-controlled trial (Anderson et al., 2002), where the extended release formulation of this drug, i.e., bupropion SR, given at doses of 300 and 400 mg/day evoked placebo-subtracted, 24-week weight reductions of 2.2% and 5.1% with sustained weight losses out to 48 weeks. In a separate study, bupropion SR in combination with a 500 kcal/day-deficit diet facilitated weight loss in obese patients with depressive symptoms (Jain et al., 2002). However, the pharmacological mechanisms responsible for the antiobesity effect of bupropion have yet to be thoroughly investigated.

Bupropion is a weak reuptake inhibitor that shows 2- to 4-fold selectivity for dopamine vs. noradrenaline, and it is inactive against 5-HT (Hyttel, 1982; Richelson and Pfenning, 1984). In our previous study in the rat, we have

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compared the thermogenic effect of bupropion with sibutramine's metabolite 2, a 5-hydroxytryptamine (5-HT) and noradrenaline reuptake inhibitor (Liu et al., 2002a). Unlike sibutramine, which reduces food intake as well as activating thermogenesis, bupropion had no effect on food intake in Wistar rats (Liu et al., 2002a), which is consistent with previous findings in man (Miller and Griffith, 1983). Bupropion increased colonic temperature and rapidly enhanced oxygen consumption in conscious rats, and its thermogenic potential was further supported by the finding that bupropion decreased the response to exogenous heat reinforcement at −8 °C (Liu et al., 2002a). However, the precise mechanism of bupropion's thermogenic property has not been pharmacologically characterised. In the present study, we have investigated the effect of bupropion on basal metabolic rate using the rigorous technique of measuring oxygen consumption in sealed chambers (indirect calorimetry) at thermoneutrality (29 °C) as described previously by Stock (1975). In addition, we have defined the relative contribution to bupropion-induced thermogenesis of noradrenaline and dopamine, and the receptor subtypes involved, by the use of various monoamine receptor antagonists.

2. Materials and methods

2.1. Animals

Experiments were performed on female Wistar rats (200–250 g at the start of the experiment). They were obtained from the colony maintained at St. George's Hospital Medical School. Animals were housed individually and maintained on a conventional pelleted stock diet with free access to water with a 12-h light cycle (lights on 0700 h) at a room temperature of 21±1 °C. All experiments were performed under the UK Animal (Scientific Procedures) Act 1986.

2.2. Chemicals

Drugs used were bupropion hydrochloride, prazosin hydrochloride, metergoline and (+)-butaclamol hydrochloride (Research Biochemicals International, St Albans, U.K.); propranolol hydrochloride (Sigma, Poole, UK); RS79948 hydrochloride [(8*aR*, 12*aS*, 13*aS*)-5,8,8*a*,9,10,11,12,12*a*,13,13*a*-decahydro-3-methoxy-12-(ethylsulphonyl)-6*H*isoquino[2,1-*g*][1,6]-naphthyridine hydrochloride] (Tocris, Bristol, UK). Bupropion was dissolved in deionised water. Propranolol was dissolved in sterile saline. Prazosin and metergoline were dissolved in minimally acidified deionised water. (+)Butaclamol was dissolved in 0.25% ethanol and RS79948 in dimethylsulphoxide (DMSO) (0.5% v/v). The antagonists employed and the doses and routes chosen are those that have been shown to be pharmacologically effective in our previous study in female Wistar rats (Liu et al., 2002b). All drugs were administered orally (gavage) using a dose volume of 5 ml/kg.

2.3. Measurement of oxygen consumption

Oxygen consumption (VO_2) was determined in closed-circuit respirometers maintained at the thermoneutral temperature for rats (29 °C). The system allows for eight rats to be individually tested at one time (Stock, 1975). Each cylindrical chamber is contained within a heated water jacket and measures 10 cm in diameter (with a flat rack in the middle for animals to rest on) and 30 cm in length. All animals were accustomed to the respirometers and procedures on two occasions the week before the experiments. There is sufficient space for the rats to turn around, but not for locomotor activity. Oxygen measurements are collected during the light phase when the rats are normally inactive and following acclimatisation sessions; the normal response of the rats is to rest or sleep when they have been placed in the calorimeter chambers. Female rats are generally chosen for the procedure for three reasons: First, they show a robust increase in thermogenesis when challenged with monoamine reuptake inhibitors (Connoley et al., 1999; Skill et al., 2000); second, females are more quiescent in the chambers than males and, therefore, provide more stable VO_2 responses (unpublished observation); and third, adult female rats have a much slower rate of growth than their male counterparts, so their weight range is not so marked when conducting crossover trials over a period of several weeks (unpublished observation). Oxygen consumption was recorded on a computer every 5 min and expressed as milliliter oxygen per kilogram metabolic body size per minute (i.e., ml/kg$^{0.75}$/min). After a 90-min measurement of baseline VO_2, animals were removed and colonic temperatures were measured using a thermocouple probe (Physiotemp, model BAT-12) inserted approximately 6 cm into the rectum. Rats were then given either vehicle or antagonists, and were returned to the chambers for 30 min before the administration of bupropion. Measurement of VO_2 was continued for a further 4 h post administration of bupropion. The 30-min averages of VO_2 were used to plot the time course of the responses and the increase in VO_2 was determined by comparing the mean of the last 30 min of the baseline readings with the mean values obtained for the posttreatment period.

2.4. Statistics

Results are presented as means±S.E.M. Statistical comparisons of the different treatment groups were made by one-way analysis of variance followed by the Dunnett's multiple comparisons test and Student's *t*-test. All probabilities quoted are two-tailed, with $P<0.05$ being taken as the level of significance.

3. Results

3.1. Effect of the nonselective 5-HT receptor antagonist, metergoline

Oxygen consumption (VO_2) in vehicle-treated animals gradually declined during the course of 4.0-h experiment (basal: 11.714±0.436 ml/kg$^{0.75}$/min; 4.0 h: 10.284±0.447 ml/kg$^{0.75}$/min, n=7). Bupropion administration (30 mg/kg, p.o.) caused a rapid rise in VO_2, with a peak stimulation of 29% at 30 min posttreatment (saline: 12.159±0.251; bupropion: 15.716±0.543; P<0.01). VO_2 remained higher during the 4-h period and pretreatment. During this period, inspection of the rats through the clear perspex end-covers to the calorimetry chambers revealed that the female Wistar rats were predominantly either quiescent or sleeping following administration of 30 mg/kg bupropion p.o. Pretreatment with the nonselective 5-HT receptor antagonist, metergoline (1 mg/kg, p.o.), had no effect on the VO_2 response induced by bupropion (Fig. 1A). The 4-h mean VO_2 (calculated as percentage of its own basal values) showed a significant increase in bupropion-treated group (P<0.01 vs. saline) and metergoline had no effect on the 4-h mean response to bupropion (Fig. 1B).

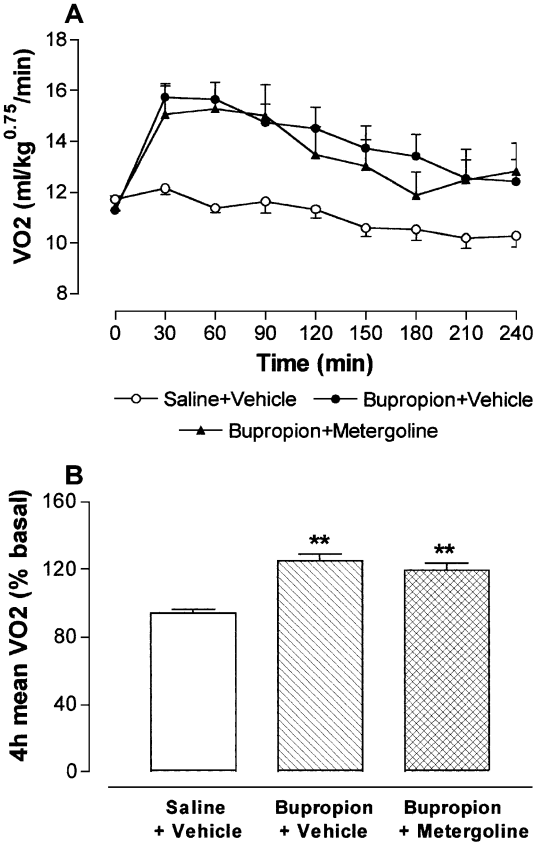

Fig. 1. Effect of the 5-HT receptor antagonist, metergoline (1 mg/kg, p.o.), on the oxygen consumption response to bupropion (30 mg/kg, p.o.). (A) Time course; (B) 4 h mean as percentage of basal. Results are mean±S.E.M., n=7–8. **P<0.01 vs. saline+vehicle (Dunnett's test).

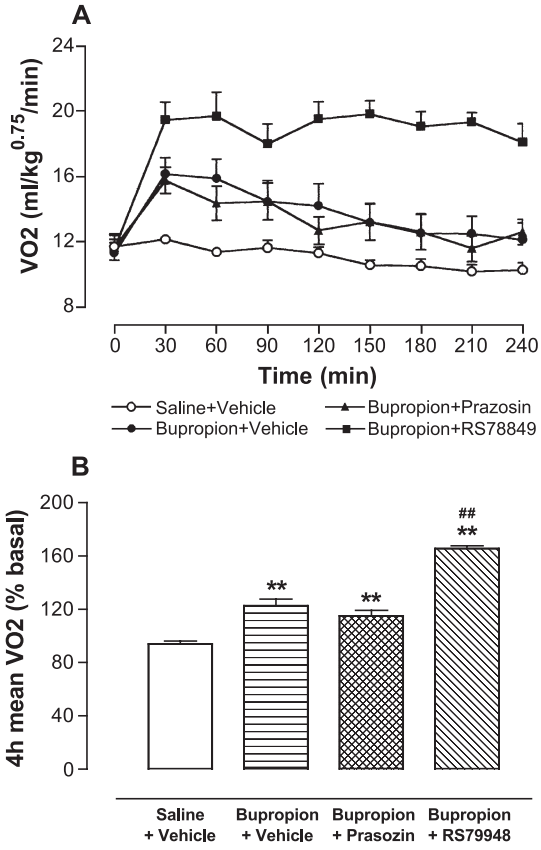

Fig. 2. Effect of the α_1-adrenoceptor antagonist, prazosin (1 mg/kg, p.o.), and α_2-adrenoceptor antagonist, RS 79948 (1 mg/kg, p.o.), on the oxygen consumption response to bupropion (30 mg/kg, p.o.). (A) Time course; (B) 4 h mean as percentage of basal. Results are mean±S.E.M., n=7–9. **P<0.01 vs. saline+vehicle; $^{\#\#}P$<0.01 vs. bupropion+vehicle (Dunnett's test).

3.2. Effect of the α_1-adrenoceptor antagonist, prazosin, and the α_2-adrenoceptor antagonist, RS79948

Bupropion (30 mg/kg, p.o.) resulted in a rapid rise in VO_2 reaching the maximal response at 30 min and the response remained elevated throughout the 4-h experimental period (Fig. 2A). The mean VO_2 during the 4-h posttreatment period was significantly higher in bupropion-treated animals as compared to that of the saline-treated group (+29%, P<0.01; Fig. 2B). Pretreatment with the α_1-adrenoceptor antagonist, prazosin (1 mg/kg, p.o.), had no effect on the VO_2 response to bupropion. However, the α_2-adrenoceptor antagonist, RS79948 (1 mg/kg, p.o.), potentiated the response, with the 4-h mean VO_2 being significantly higher than that of bupropion-treated group (P<0.01; Fig. 2B).

3.3. Effect of the nonselective β-adrenoceptor antagonist, propranolol

Pretreatment with a low-dose propranolol (1 mg/kg, p.o.) to block β_1- and β_2-adrenoceptors had no effect on the VO_2 response to bupropion (30 mg/kg, p.o.; Fig. 3A,B). However, a high dose of propranolol (20 mg/kg, p.o.),

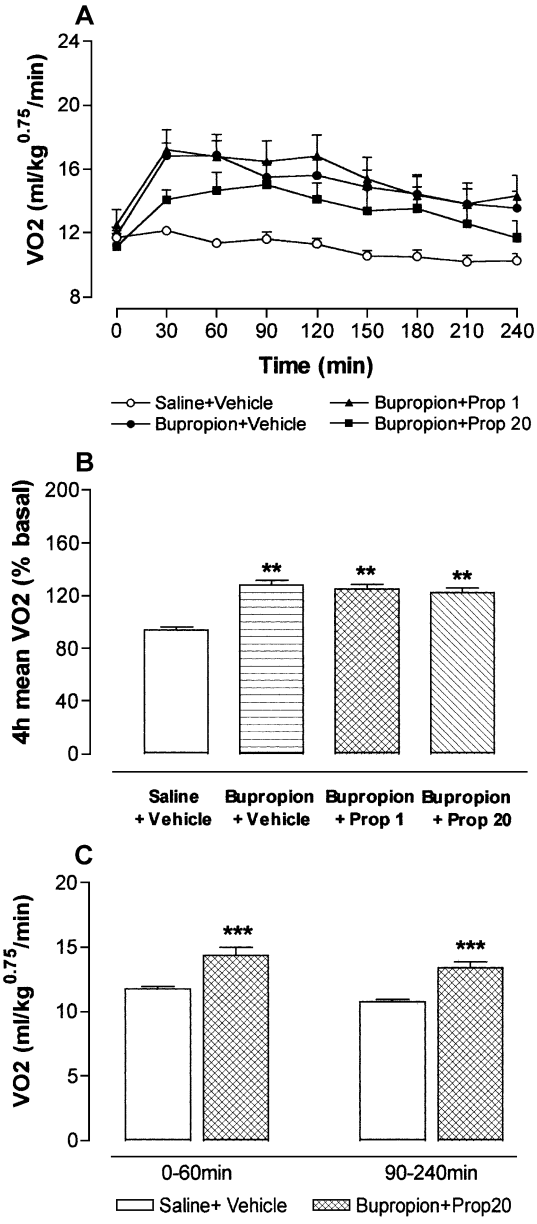

Fig. 3. Effect of the nonselective β-adrenoceptor antagonist, propranolol (1 and 20 mg/kg, p.o.), on the oxygen consumption response to bupropion (30 mg/kg, p.o.). (A) Time course; (B) 4 h mean as percentage of basal. Results are mean±S.E.M., n=6–10. **P<0.01 vs. saline+vehicle (Dunnett's test). (C) Responses at 0–60 and 90–240 min for bupropion+propranolol (20 mg/kg) vs. saline+vehicle, ***P<0.001 (unpaired t test).

sufficient to block β_3-adrenoceptors in addition to the β_1- and β_2-adrenoceptor subtypes, significantly inhibited the response during the first 60 min. The mean VO_2 for the first 60 min was 17.35±0.76 ml/kg$^{0.75}$/min for bupropion-treated and 14.38±0.63 ml/kg$^{0.75}$/min (−18%; P<0.01) for the animals pretreated with propranolol (20 mg/kg, p.o.). This reduction was of relatively short duration so that when the 4-h mean VO_2 results, expressed as percentage change over basal values, are presented, no significant difference between the bupropion-treated and bupropion+propranolol-treated animals was observed (Fig. 3B). Despite the 18% inhibition of the bupropion response by the high dose of propranolol during the first 60 min, oxygen consumption remained significantly higher in the bupropion+propranolol (20 mg/kg)-treated group compared with the saline+vehicle-treated controls for 0–60 min and 90–240 min post bupropion administration (P<0.001; Fig. 3C).

3.4. Effect of the dopamine D2/D1 receptor antagonist, (+)butaclamol

Pretreatment with the nonselective dopamine D2/D1 receptor antagonist, butaclamol (200 μg/kg, p.o.), caused a

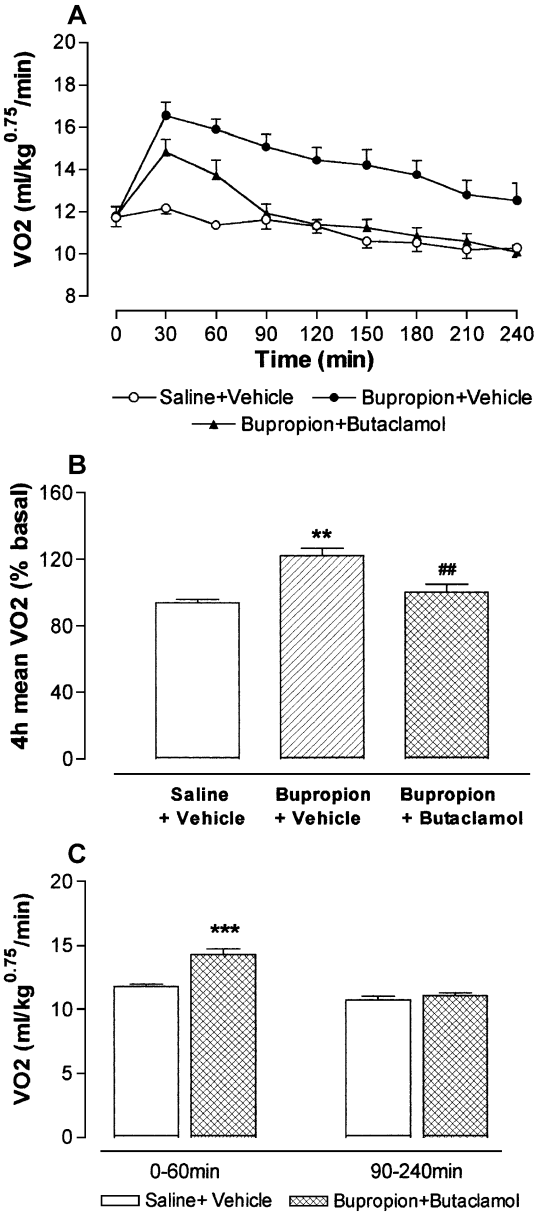

Fig. 4. Effect of dopamine D2/D1 receptor antagonist, (+)butaclamol (200 μg/kg, p.o.), on oxygen consumption response to bupropion (30 mg/kg, p.o.). (A) Time course; (B) 4 h mean as percentage of basal. Results are mean±S.E.M., n=7–8. **P<0.01 vs. saline+vehicle; ##P<0.01 vs. bupropion+vehicle (Dunnett's test). (C) Responses at 0–60 and 90–240 min for bupropion+(+)butaclamol (200 μg/kg) vs. saline+vehicle, ***P<0.001 (unpaired t test).

significant, 12% inhibition of the VO_2 response to bupropion during the first 60 min (bupropion: 16.21±0.39 vs. bupropion+butaclamol: 14.27±0.47 ml/kg$^{0.75}$/min; $P<0.01$). However, it still remained significantly higher ($P<0.001$) than that of saline+vehicle-treated animals for 0–60 min (Fig. 4C). The effect of bupropion on VO_2 between 90 and 240 min was completely blocked by (+)butaclamol as the response was not different from the saline-treated animals (Fig. 4A,C). When the 4-h mean VO_2 response (expressed as percentage of basal) was calculated, there was a significant increase of VO_2 in bupropion-treated ($P<0.01$), but not in the bupropion+(+)butaclamol-treated animals (Fig. 4B).

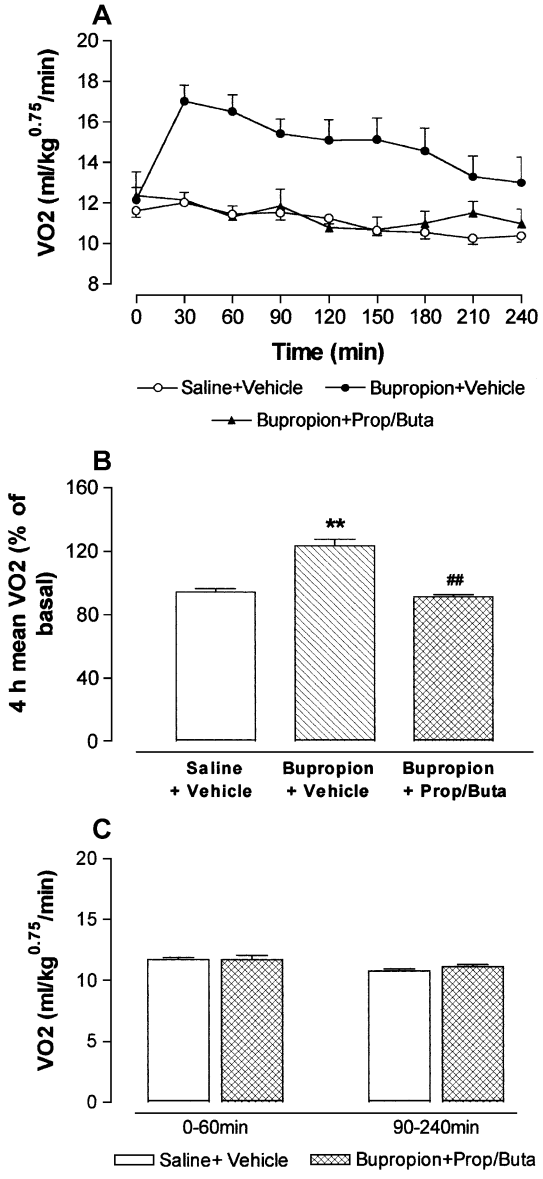

Fig. 5. Effect of a high dose of the nonselective β-adrenoceptor antagonist, propranolol (20 mg/kg, p.o.), and dopamine D2/D1 receptor antagonist, (+)butaclamol (200 μg/kg, p.o.), on oxygen consumption response to bupropion (30 mg/kg, p.o.). (A) Time course; (B) 4 h mean as percentage of basal. Results are mean±S.E.M., n=6–10. **$P<0.01$ vs. saline+vehicle; $^{\#\#}P<0.01$ vs. bupropion+vehicle (Dunnett's test). (C) Responses at 0–60 and 90–240 min for bupropion+(+)butaclamol/propranolol vs. saline+vehicle.

3.5. Combination effect of propranolol and (+)butaclamol

Co-administration of a high dose of propranolol (20 mg/kg, p.o.) to block all β-adrenoceptor subtypes and (+)butaclamol (200 μg/kg, p.o.) to block dopamine D2/D1 receptors abolished the increase in VO_2 induced by bupropion (30 mg/kg, p.o.) over the whole time course of the experiment (Fig. 5A). The mean VO_2 over the 4-h period (expressed as percentage of basal) of the bupropion+(+)butaclamol group was significantly lower than that of the group treated with bupropion alone ($P<0.01$); moreover, the former was also not significantly different from the VO_2 response of the saline-treated controls (Fig. 5B). Unlike the high dose of propranolol (20 mg/kg, p.o.) or (+)butaclamol (200 μg/kg, p.o.) alone, which caused partial inhibition of the VO_2 response during the first 60 min, the combination of both antagonists completely prevented the rise in VO_2 because no significant difference was found between the bupropion+propranolol/(+)butaclamol-treated and saline+vehicle-treated groups at 0–60 min and 90–240 min (Fig. 5C).

4. Discussion

Results from the present study demonstrate a potent thermogenic effect of bupropion as indicated by the rapid and sustained increase in oxygen consumption. The gradual decline of oxygen consumption in the saline-treated animals over the 4-h experimental period was probably due to a decrease in meal-induced thermogenesis. This is because rats are nocturnal feeders and oxygen consumption measurements were made during the light cycle with the rats having no access to food.

The nonselective 5-HT receptor antagonist, metergoline, had no effect on the increase in oxygen consumption produced by bupropion, demonstrating that 5-HT is not involved in the production of thermogenesis by this monoamine reuptake inhibitor. This observation is consistent with the finding that bupropion does not inhibit the reuptake of 5-HT into rat brain synaptosomes (Hyttel, 1982; Richelson and Pfenning, 1984). Metergoline (1 mg/kg) was adequate to attenuate 5-HT receptor function because we have previously shown that this dose is sufficient to abolish the thermogenic response to one of sibutramine's active metabolites, i.e., Metabolite 2 (Liu et al., 2002b).

Previous studies have demonstrated that activation of α_1-adrenoceptors, in addition to β-adrenoceptors, contributes to noradrenaline-induced thermogenesis by increasing cytosolic Ca^{2+} level (Zhao et al., 1997), and, for example, Stock (1997) suggested that simultaneous indirect stimulation of α_1- and β_3-adrenoceptors plays an important role in the thermogenic actions of the serotonin and noradrenaline

reuptake inhibitor, sibutramine. However, results from the present study showed no involvement of α_1-adrenoceptor activation in bupropion-induced thermogenesis because the selective antagonist, prazosin, when given at a dose sufficient to prevent the thermogenic response to Metabolite 2 (Liu et al., 2002b), did not attenuate the increase in oxygen consumption evoked by bupropion. On the other hand, the α_2-adrenoceptor antagonist, RS79948, potentiated this effect as shown by the higher 4-h mean oxygen consumption in the bupropion+RS79948-treated compared with the bupropion+vehicle-treated animals. Enhancement of thermogenesis by α_2-adrenoceptor antagonists has previously been demonstrated whereby yohimbine increased sympathetic tone and stimulated lipolysis in dogs (Galitzky et al., 1991). Moreover, in our previous study, we observed that RS79948 increased the colonic temperature of rats (Liu et al., 2002b). To investigate the role of β-adrenoceptors in bupropion-induced oxygen consumption, both low (1 mg/kg) and high (20 mg/kg) dose of the nonselective β-adrenoceptor antagonist, propranolol, were employed. The low dose is believed to be sufficient to block β_1- and β_2-sutypes without affecting the β_3-adrenoceptor (Carlisle and Stock, 1992), whereas a high dose of 20 mg/kg is required to block β_3-adrenoceptors in addition to the other two β-subtype populations (Liu et al., 2002b; Carlisle and Stock, 1992). Results showed that blocking the β_1- and β_2-adrenoceptors with the low dose propranolol had no effect on the bupropion-induced increase in oxygen consumption, indicating that these subtypes are not mediators of this drug's thermogenic effect. However, the high dose of propranolol, which blocked β_3- as well as β_1- and β_2-adrenoceptors, significantly inhibited the oxygen consumption response to bupropion over the first 60 min. During the later period (90–240 min), the response was not significantly attenuated, suggesting that β_3-adrenoceptor activation contributes particularly to bupropion-induced thermogenesis during the initial phase after drug administration. Although for consistency with our previous thermogenesis studies in female Wistar rats (Liu et al., 2002b), propranolol was used to block β_3-adrenoceptors in the current series of experiments, this ligand also has the disadvantage of simultaneously blocking β_1- and β_2-adrenoceptors. A highly selective β_3-adrenoceptor antagonist, i.e., SR 59230A (3-(2-ethylphenoxy)-1-{[(1*S*)-1,2,3,4,-tetrahydronaphth-1-yl]amino}-(2*S*)-propanol oxylate), is now commercially available and it will be useful in future experiments to confirm the results obtained with propranolol using SR 59230A.

To test the relative dopaminergic contribution, the nonselective dopamine D2/D1 receptor antagonist, (+)butaclamol, was administered prior to bupropion. (+)Butaclamol partially, but significantly, inhibited the oxygen consumption response during the first 60 min, and it completely blocked the response between 90 and 240 min. This finding indicates that dopamine is an important monoamine mediator of bupropion-induced thermogenesis and reuptake inhibition is almost certainly the pharmacological mechanism responsible for this effect (Hyttel, 1982; Richelson and Pfenning, 1984). Whilst these experiments clearly implicate a role for dopamine receptor activation in bupropion's thermogenic action, the subtypes responsible have not been defined. It is now well accepted that in the dopamine receptor superfamily, there are two subtypes D1-like, i.e., D1 and D5, and three subtypes of D2-like, i.e., D2, D3 and D4, receptors (see review by Missale et al., 1998). Hence, the important next step will be to use selective antagonists to define which dopamine receptor subtype(s) mediate bupropion's thermogenic effect. Additional interest has been added to this question, by the observation that D1 receptor activation may play an important role in switching blood supply between various vascular beds (Guzman et al., 2002).

The involvement of both β_3-adrenergic and dopamine D2/D1 receptors during the initial phase after bupropion administration was evident because co-administration of a high-dose of propranolol (20 mg/kg) and (+)butaclamol abolished the increase in oxygen consumption over the first 60 min. In synaptosomal preparations, bupropion is a weak inhibitor of dopamine reuptake with 2- to 4-fold selectivity over noradrenaline (Hyttel, 1982; Richelson and Pfenning, 1984; see also Ascher et al., 1995 for a review). Bupropion's in vivo profile (dopamine>noradrenaline) was confirmed by the finding that, unlike potent noradrenaline reuptake inhibitors, bupropion does not prevent ptosis in rats induced by reserpine (Heal et al., 1992), but it can reverse the sedation and ptosis induced by the less severe monoamine depleting agent, tetrabenazine (Soroko et al., 1977). Bupropion's dopaminergic property was also demonstrated by its ability to increase spontaneous locomotor activity in rodents (Nomikos et al., 1992) and to increase extraneuronal dopamine concentrations as determined by in vivo intracerebral microdialysis (Nomikos et al., 1992; Li et al., 2002). Although dopaminergic systems in the medial hypothalamus are suggested to contribute to the regulation of food intake and feeding pattern (see Meguid et al., 2000 for review), we failed to detect any effect of bupropion on food consumption (Liu et al., 2002a). Moreover, although drugs like *d*-amphetamine with pronounced central dopaminergic actions reduce food intake partly through activation of dopamine D2 receptors (Mitchell et al., 1998), this effect is nonspecific being a secondary consequence of behavioural and locomotor hyperactivity (Halford et al., 1998). Dopaminergic drugs, therefore, appear to have little influence on the physiological control of appetite and satiety.

Overall, it can be concluded that bupropion stimulates thermogenesis in rats by a combined action to enhance dopaminergic drive via dopamine D2 and/or D1 receptor activation. Because this response is attenuated by β_3-adrenoceptor blockade, brown adipose tissue is almost certainly the effector. The potentiation of bupropion-induced thermogenesis by RS74998 indicates that blockade of terminal α_2-adrenoceptors can effectively augment sympa-

thetic outflow onto β_3-adrenoceptors mediating this effect. However, the failure of prazosin and low-dose propranolol to modify bupropion-induced thermogenesis rules out activation of α_1-, β_1- and β_2-adrenoceptor systems as having a role in its thermogenic action. What is apparent from the additive effects of high dose propranolol and (+)butaclamol and their different time courses of effect on bupropion-induced thermogenesis is that activation of both noradrenergic and dopaminergic systems are operating in tandem in the production of this response. What is presently unclear is whether bupropion has both a central and peripheral action to stimulate thermogenesis. Because we have previously reported that bupropion does not significantly attenuate food intake in rats (Liu et al., 2002a), these data further confirm that this drug's weight-reducing effect is predominantly due to its thermogenic action. Moreover, because bupropion is similarly reported to have no hypophagic effect in man (Miller and Griffith, 1983), these data suggest that the antiobesity or weight-reducing property of bupropion in the human studies (Jain et al., 2002; Anderson et al., 2002; Jorenby et al., 1999) may be due to a thermogenic action. If the pharmacological characterisation of bupropion-induced thermogenesis in rats has relevance to man, then the findings implicate the activation of dopamine D2/D1 receptors (and possibly also β_3-adrenoceptors) as potential mediators of the effect.

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References

Anderson, J.W., Greenway, F.L., Fujioka, K., Gadde, K.M., McKenney, J., O'Neil, P.M., 2002. Bupropion SR enhances weight loss: a 48-week double-blind, placebo-controlled trial. Obes. Res. 10, 633–641.

Ascher, J.A., Cole, J.O., Colin, J.-N., Feighner, J.P., Ferris, R.M., Fibiger, H.C., Golden, R.N., Martin, P., Potter, W.Z., Richelson, E., Sulser, F., 1995. Bupropion: a review of its mechanism of antidepressant activity. J. Clin. Psychiatry 56, 395–401.

Carlisle, H.J., Stock, M.J., 1992. Potentiation of thermoregulatory responses to isoproterenol by β-adrenergic antagonists. Am. J. Physiol. 263, R915–R923.

Connoley, I.P., Liu, Y.L., Frost, I., Reckless, I.P., Heal, D.J., Stock, M.J., 1999. Thermogenic effects of sibutramine and its metabolites. Br. J. Pharmacol. 126, 1487–1495.

Galitzky, J., Vermonel, M., Lafontan, M., Montastruc, P., Berlan, M., 1991. Thermogenic and lipolytic effect of yohimbine in the dog. Br. J. Pharmacol. 104, 514–518.

Guzman, J.A., Rosado, A.E., Kruse, J.A., 2002. Dopamine-1 receptor stimulation impairs intestinal oxygen utilization during critical hypofusion. Am. J. Heart Circ. Physiol. 284, H668–H675.

Halford, J.C.G., Wanninayake, S.C.D., Blundell, J.E., 1998. Behavioral satiety sequence (BSS) for the diagnosis of drug action on food intake. Pharmacol. Biochem. Behav. 61, 159–168.

Heal, D.J., Frankland, A.T.J., Gosden, J., Hutchins, L.J., Prow, M.R., Luscombe, G.P., Buckett, W.R., 1992. A comparison of sibutramine hydrochloride, bupropion and methamphetamine on dopaminergic function: evidence that dopamine is not a pharmacological target for sibutramine. Psychopharmacology 107, 303–309.

Hughes, J.R., 2000. New treatments for smoking cessation. Can. Cancer J. Clin. 50, 143–151.

Hyttel, J., 1982. Citalopram—Pharmacological profile of a specific serotonin uptake inhibitor with antidepressant activity. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 6, 277–295.

Jain, A.K., Kaplan, R.A., Gadde, K.M., Wadden, T.A., Allison, D.B., Brewer, E.R., Leadbetter, R.A., Richard, N., Haight, B., Jamerson, B.D., Buaron, K.S., Metz, A., 2002. Bupropion SR vs. placebo for weight loss in obese patients with depressive symptoms. Obes. Res. 10, 1049–1056.

Jorenby, D.E., Leischow, S.J., Nides, M.A., Rennard, S.I., Johnston, J.A., Hughes, A.R., Smith, S.S., Muramoto, M.L., Daughton, D.M., Doan, K., Fiore, M.C., Baker, T.B., 1999. A controlled trial of sustained-release bupropion, a nicotine patch, or both for smoking cessation. N. Engl. J. Med. 340, 685–691.

Li, S.X., Perry, K.W., Wong, D.T., 2002. Influence of fluoxetine on the ability of bupropion to modulate dopamine and norepinephrine concentrations in three mesocorticolimbic areas of rats. Neuropharmacology 42, 181–190.

Liu, Y.L., Connoley, I.P., Harrison, J., Heal, D.J., Stock, M.J., 2002a. Comparison of the thermogenic and hypophagic effects of sibutramine's metabolite 2 and other monoamine reuptake inhibitors. Eur. J. Pharmacol. 452, 49–56.

Liu, Y.L., Heal, D.J., Stock, M.J., 2002b. Mechanism of the thermogenic effect of Metabolite 2 (BTS 54 505), a major pharmacologically active metabolite of the novel anti-obesity drug, sibutramine. Int. J. Obes. 26, 1245–1253.

Meguid, M.M., Fetissov, S.O., Varma, M., Sato, T., Zhang, L., Laviano, A., Rossi-Fanelli, F., 2000. Hypothalamic dopamine and serotonin in the regulation of food intake. Nutrition 16, 843–857.

Miller, L., Griffith, J., 1983. A comparison of bupropion, dextroamphetamine, and placebo in mixed-substance abusers. Psychopharmacology 80, 199–205.

Mitchell, J.C., Jackson, H.C., Heal, D.J., 1998. Effect of monoamine antagonists on aminorex, phentermine and *d*-amphetamine hypophagia. J. Psychopharmacol. 12 (Suppl. A), A38.

Missale, C., Nash, S.R., Robinson, S.W., Jaber, M., Caron, M.G., 1998. Dopamine receptors; from structure to function. Physiol. Rev. 78, 189–225.

Nomikos, G.G., Damsma, G., Wenkstern, D., 1992. Effects of chronic bupropion on interstitial concentrations of dopamine in rat nucleus accumbens and striatum. Neuropsychopharmacology 7, 7–14.

Richelson, E., Pfenning, M., 1984. Blockade by antidepressants and related compounds of biogenic amine uptake into rat brain synaptosomes: most antidepressants selectively block norepinephrine uptake. Eur. J. Pharmacol. 104, 227–286.

Settle, E.C., Stahl, S.M., Batey, S.R., Johnston, J.A., Ascher, J.A., 1999. Safety profile of sustained-release bupropion in depression: results of three clinical trials. Clin. Ther. 21, 454–463.

Skill, M.J., Dickinson, K., Jones, R.B., Heal, D.J., 2000. Thermogenic effect of chronic sibutramine treatment in female Wistar rats. Br. J. Pharmacol. 129, 143.

Soroko, F.E., Mehta, N.B., Maxwell, R.A., 1977. Bupropion hydrochloride: [(±)alpha-*t*-butylamino-3-chloropropiophenone HCI]: a novel antidepressant agent. J. Pharm. Pharmacol. 29, 767–770.

Stock, M.J., 1975. An automatic, closed-circuit oxygen consumption apparatus for small animals. J. Appl. Physiol. 39, 849–850.

Stock, M.J., 1997. Sibutramine: a review of the pharmacology of a novel anti-obesity agent. Int. J. Obes. 21 (Suppl. 1), S25–S29.

Zhao, J., Cannon, B., Nedergaard, J., 1997. α_1-Adrenergic stimulation potentiates the thermogenic action of β3-adrenoceptor-generated cAMP in brown fat cells. J. Biol. Chem. 272, 32847–32856.