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Enantioselective behavioral effects of sibutramine metabolites

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Abstract

The anti-obesity agent, racemic (*RS*)-sibutramine, has two active metabolites, desmethylsibutramine and didesmethylsibutramine. To the extent that sibutramine itself mediates some of its side effects, desmethylsibutramine and/or didesmethylsibutramine might be safer and just as therapeutically effective. Because both desmethylsibutramine and didesmethylsibutramine are also optically active, the present study assessed the anorexic effects (2.5–10 mg/kg, i.p., for all drugs), in rats, of the *R*(+)-and *S*(−)-enantiomers of both metabolites and compared them to the effects of racemic sibutramine. Locomotor activity (2.5–10 mg/kg, i.p., for all drugs), a dopamine dependent behavior, was also measured in view of some uncertainty regarding dopaminergic effects of sibutramine. In view of sibutramine's antidepressant profile in animal models, the same drugs were also tested in the Porsolt swim test (0.1–2.5 mg/kg, i.p., for all drugs). Lastly, the IC_{50}s of all drugs to inhibit uptake in vitro of norepinephrine, serotonin and dopamine were determined. Both (*R*)-enantiomers had significantly greater anorexic effects than those of their respective (*S*)-enantiomers as well as of sibutramine. All of the agents increased locomotor activity and reduced immobilized time (''behavioral despair'') in the swim test; again, the (*R*)-enantiomers were more potent than the (*S*)-enantiomers and sibutramine. However, the anorexic and locomotor effects could be dissociated from each other as well as from effects in the swim test. Both (*R*)-desmethylsibutramine and (*R*)-didesmethylsibutramine as well as sibutramine decreased food intake at a time (24–42 h post-treatment) when locomotor activity was unaffected. All of the drugs appeared to be more potent in the swim test than in the other tests and all of the drugs were more potent at inhibiting uptake of norepinephrine and dopamine than of serotonin. The results suggest that these enantioselective metabolites of sibutramine could be safe and effective treatments for obesity as well as possibly for depression.

Keywords: Sibutramine; Desmethylsibutramine; Didemethylsibutramine; Food intake; Obesity; Locomotor activity; Antidepressant

1. Introduction

Racemic sibutramine is a monoamine reuptake inhibitor that is presently being marketed as an anti-obesity agent. The pharmacological effects of sibutramine are mostly attributable to its more active secondary and primary amine metabolites, desmethylsibutramine and didesmethylsibutramine, respectively (e.g., Luscombe et al., 1989; Heal et al., 1998). Although both metabolites are potent inhibitors of the reuptake of serotonin, norepinephrine and dopamine in vitro, the results of in vivo studies have indicated that there is some selectivity for serotonin and norepinephrine relative to dopamine (Luscombe et al., 1989) and that, at therapeutic doses, dopaminergic systems are not affected (Heal et al., 1992). Thus, the weight loss produced by sibutramine is thought to be due to a combination of serotonin- and norepinephrine-mediated mechanisms that increase both satiety and energy expenditure (Jackson et al., 1997a,b; Stock, 1997; Heal et al., 1998).

Sibutramine has several side effects, perhaps the most problematic of which is hypertension. Sibutramine itself, because it has at least 10-fold selectivity in vitro for inhibiting reuptake of norepineprhine relative to serotonin (Luscombe et al., 1989; Cheetham et al., 1993; Stock, 1997), may contribute to the hypertension, and it is possible that the metabolites desmethylsibutramine and

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Table 1
Effects of (*RS*)-sibutramine, (*R*)-desmethylsibutramine, (*S*)-desmethylsibutramine, (*R*)-didesmethylsibutramine and (*S*)-didesmethylsibutramine on monoamine uptake

	Functional uptake IC_{50} values (nM)		
	Norepinephrine	Serotonin	Dopamine
(*RS*)-sibutramine	350	2800	1200
(*R*)-desmethylsibutramine	4	44	12
(*S*)-desmethylsibutramine	870	9200	180
(*R*)-didesmethylsibutramine	13	140	8.9
(*S*)-didesmethylsibutramine	62	4300	12

didesmethylsibutramine might be safer anti-obesity agents. Furthermore, desmethylsibutramine and didesmethylsibutramine are both optically active, and potency and well as safety might be increased if their therapeutic effects exhibit enantioselectivity. In the present study we have compared the anorexic effects of the *R*(+)- and *S*(−)-enantiomers of desmethylsibutramine and didesmethylsibutramine to each other and to racemic sibutramine. In addition, although the importance of dopaminergic effects of sibutramine and its metabolites has been minimized (Heal et al., 1992, 1998), we also assessed the possibility that one or more of these agents might have a locomotor stimulant effect, a well established dopamine dependent behavior (e.g., Wise and Bozarth, 1987). This was done in view of the in vitro potencies of desmethylsibutramine and didesmethylsibutramine to inhibit dopamine reuptake (Luscombe et al., 1989; Heal et al., 1998; Table 1) and of sibutramine's in vivo efficacy to increase extracellular levels of dopamine in the nucleus accumbens (Martin et al., 1995). Lastly, because sibutramine has an antidepressant profile in animal models (Buckett et al., 1988), the same agents were also tested in the Porsolt swim test (Porsolt et al., 1977) of ''behavioral despair'', a frequently used screening procedure for assessing potential antidepressant-like activity.

2. Materials and methods

2.1. Materials

Naïve male Long-Evans derived rats (250–275 g; Charles River, NY), used for all studies, were maintained on a normal 12-h light cycle (lights on at 7:00 a.m., lights off at 7:00 p.m.). For all animal experiments the ''Principles of laboratory animal care'' (NIH publication No. 85-23, revised 1985) were followed.

The hydrochloride salts of sibutramine, (*R*)-desmethylsibutramine, (*S*)-desmethylsibutramine, (*R*)-didesmethylsibutramine, and (*S*)-didesmethylsibutramine were all supplied by Sepracor, Marlborough, MA, USA. All drugs (chemical and enantiomeric purities $> 99\%$) were dissolved in a physiological saline vehicle.

2.2. Determination of monoamine uptake in vitro

The functional uptake of norepinephrine, serotonin (Perovic and Müller, 1995) and dopamine (Janowsky et al., 1986) was performed at Cerep (Le Bois l'Eveque, 86600 Celle L'Evescault, France) using synaptosomes isolated (in sucrose buffer) from male Wistar rat hypothalamus, whole brain, or corpus striatum, respectively.

Synaptosomes and [^{3}H]-monoamines were prepared in Krebs' buffer, which was oxygenated and then incubated in a deep well plates. Uptake was performed by incubating the synaptosomes in the presence and absence of each of the test compounds. Uptake was then stopped by filtration through a unifilter 96-well plate, which was washed with Krebs buffer in order to eliminate the free radiolabeled monoamine. Radioactivity taken up by synaptosomes was retained on the filter and then measured with a microplate scintillation counter.

Standards, or reference compounds, used were protriptyline, imipramine, and GRB12909 for norepinephrine, serotonin, and dopamine, respectively. Test compounds were tested initially at 10 mM in duplicate, and if at least 50% inhibition of uptake was observed, they were tested further at eight different concentrations in duplicate in order to obtain full inhibition curves. IC_{50}-values (concentration inhibiting control activity by 50%) were then determined by nonlinear regression of the inhibition curves.

2.3. Measurement of food and water intake and body weight

To measure food intake, individually housed rats were allowed to consume ad libitum powdered rat chow from jars specially designed to eliminate problems of spillage (Joy et al., 1967). Ad libitum water intake was measured with water tubes constructed from 50 ml syringes fitted with non-leaking ball-valve spouts. Rats were allowed to acclimate to the food jars for three days before measurements were begun. Thereafter, body weights, feeding jar weights (after being filled), and water levels (after filling tubes) were recorded at 4:00 p.m. and at 10 a.m.; changes in body weight and food and water consumption were therefore measured over an 18 h time period that included the entire nocturnal, ''lights off'' part of the diurnal cycle. After obtaining two days of baseline results, rats were administered one of the following treatments (all injected i.p.; $N = 6$/dose/group) immediately following the recording of the 4:00 p.m. data: saline vehicle (1 ml/kg), sibutramine (2.5, 5, 10 mg/kg), (*R*)-desmethylsibutramine (2.5, 5, 10 mg/kg), (*S*)-desmethylsibutramine (2.5, 5, 10 mg/kg), (*R*)-didesmethylsibutramine (2.5, 5, 10 mg/kg), and (*S*)-didesmethylsibutramine (2.5, 5, 10 mg/kg). Food and water intake and body weight were measured again for two nights after the initial post-treatment night.

All drugs were assessed concurrently; each batch of 12–15 rats being tested each day included representatives

from each drug group such that all groups were counterbalanced across days.

2.4. Measurement of locomotor activity

Other groups ($N = 5–10$/group) of naïve rats were used to assess the effects of the same drugs on locomotor activity (testing conducted between 1:00 and 5:00 p.m.); three dosages (2.5, 5.0 or 10.0 mg/kg, i.p.) of each agent were studied and separate groups were used for each dosage of each treatment. Locomotor activity was measured in eight cylindrical (60 cm diameter) photocell activity cages, each having three intersecting infrared light beams; each time a light beam was broken a single activity count was recorded on an IBM-compatible computer with Med Associates software. With one exception (see results), testing generally began immediately following injections and lasted 2 h; rats had no pre-drug exposure to the test environment. All drugs were assessed concurrently; each batch of eight rats being tested included representatives from each drug group such that all groups were counterbalanced across days.

2.5. Measurement of ''behavioral despair'' (Porsolt swim test)

Other groups ($N = 6$/group) of naïve rats were used to assess the effects of the same drugs in the Porsolt test;

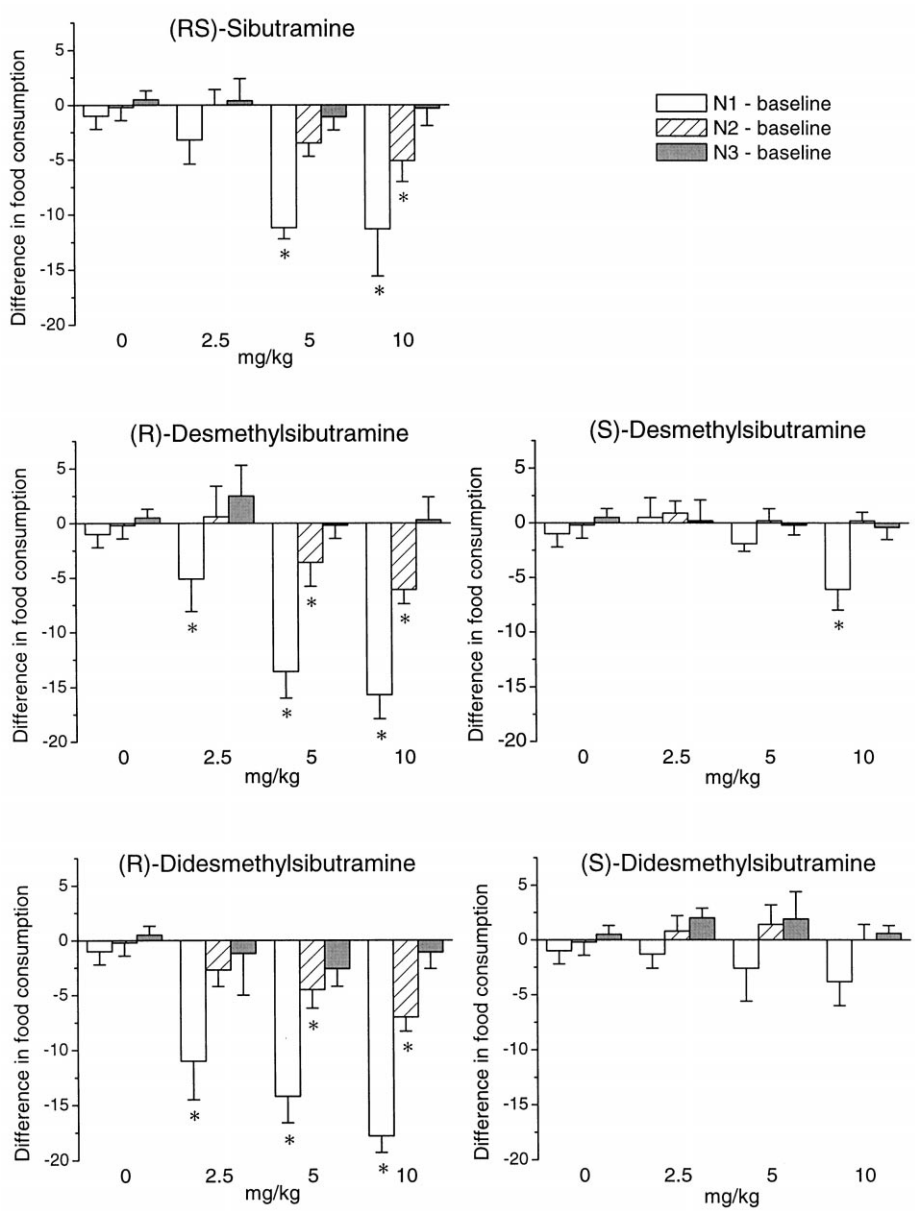

Fig. 1. Treatment (all $N = 6$/group; means ± S.E.M.) effects on food intake in terms of differences from baseline (bas) values (average of two nights preceding drug administration) over each nightly (4:00 p.m.–10:00 a.m.) test period (N1, N2 and N3 refer to first, second and third nights after drug administration, respectively); * [drug vs. vehicle] indicate significant differences ($P < 0.05$, Newman–Keuls post-hoc tests).

three dosages (0.1, 0.5 or 2.5 mg/kg, i.p.) of each agent were studied and separate groups were used for each dosage of each treatment. Rats were individually placed in a Plexiglas cylindrical swimming tank (height 50 cm, diameter 22 cm) containing 25°C water. The water level was determined by the size of the rat and ranged from 18–22 cm. The water was filled to a point where only the extreme tips of rats' hind toes could skim the bottom of the tank. Fresh water was replaced before and after each rat was in the tank.

Each rat was initially exposed to the swimming tank for 15 min; upon removal from the tank, rats were placed in an enclosed area heated to 32°C. Following a 15 min drying period, the first of a series of three intraperitoneal injections (same drug and same dose) was administered. The three injections were timed to occur 24 h, 5 h and 1 h prior to testing on the next day. Testing consisted of returning the rat to the same swimming tank for 5 min; using a Panasonic 3260 video camera, the behavior of each rat was recorded during the test period.

The percent of time that the rat was mobile versus time immobile was blindly scored from the videotapes. A mobile movement score was characterized by one or more of the following actions; flaring arms, scratching walls, diving below surface, turning in circles, and skimming the sides of the tank. An immobile score was characterized by one or more of the following: nose slightly above water, limbs and tail either completely still or used only to

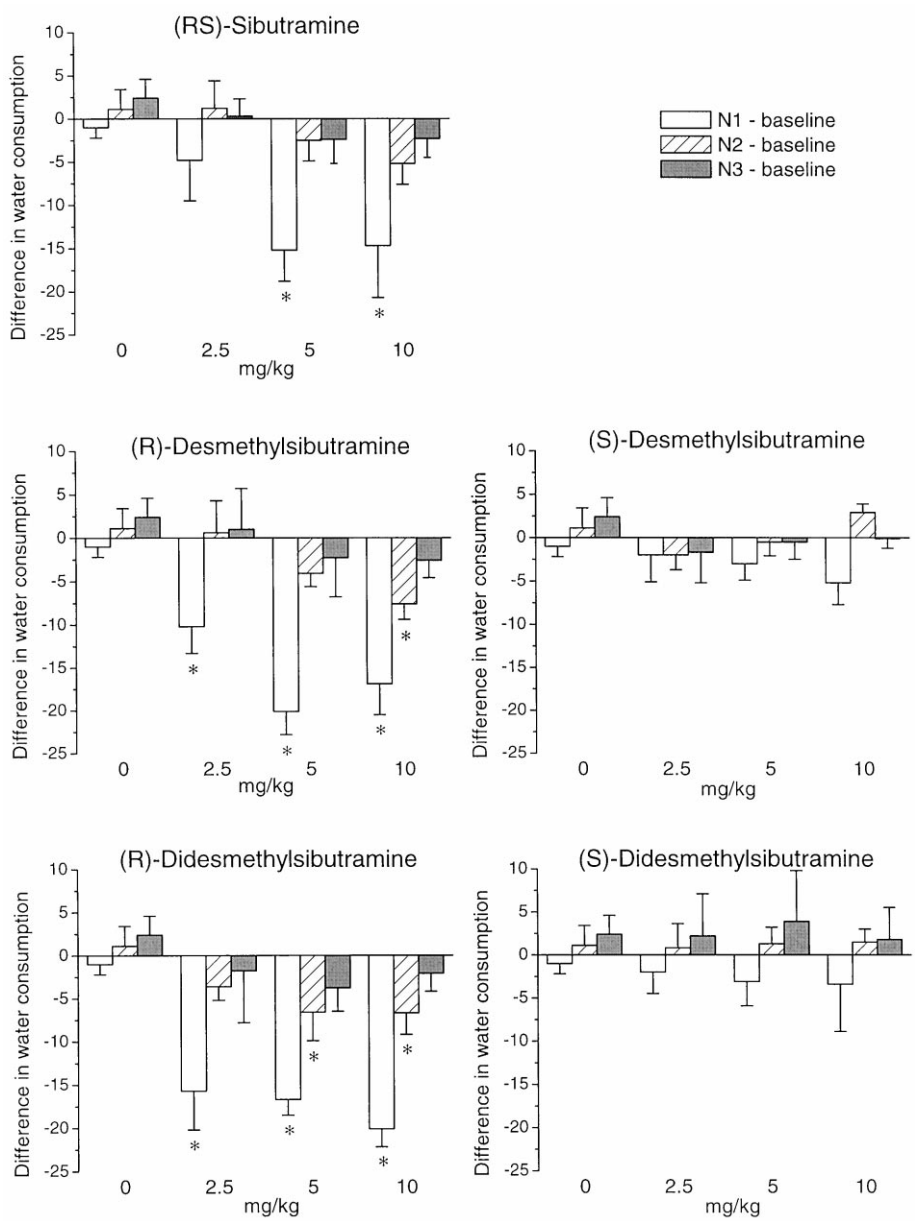

Fig. 2. Treatment (all $N = 6$/group; means ± S.E.M.) effects on water intake in terms of differences from baseline (bas) values (average of two nights preceding drug administration) over each nightly (4:00 p.m.–10:00 a.m.) test period (N1, N2 and N3 refer to first, second and third nights after drug administration, respectively); * [drug vs. vehicle] indicate significant differences ($P < 0.05$, Newman–Keuls post-hoc tests).

maintain balance, and slight bobbing to keep head above water.

All drugs were assessed concurrently; each batch of rats being tested each day included representatives from each drug group such that all groups were counterbalanced across days.

3. Results

3.1. Effects on monoamine uptake

As shown in Table 1, the (*R*)-enantiomers of both metabolites and the (*S*)-enantiomer of didesmethylsibutramine all had low nM IC_{50}s for inhibiting uptake of norepinephrine and dopamine. All compounds were more potent at inhibiting uptake of norepinephrine and dopamine than of serotonin.

3.2. Effects on food and water intake and body weight

The average (±S.E.M.) food intake (g) and water intake (ml) of the various groups on the two nights (4:00 p.m.–10:00 a.m.) preceding drug administration ranged from 22.8 ± 1.3 to 25.8 ± 1.7 and 30.6 ± 2.9 to 34.2 ± 3.8, respectively; the average body weights (g) of the various groups immediately prior to drug administration ranged from 298.8 ± 5.6 to 310.7 ± 7.2. Figs. 1–3 shows treat-

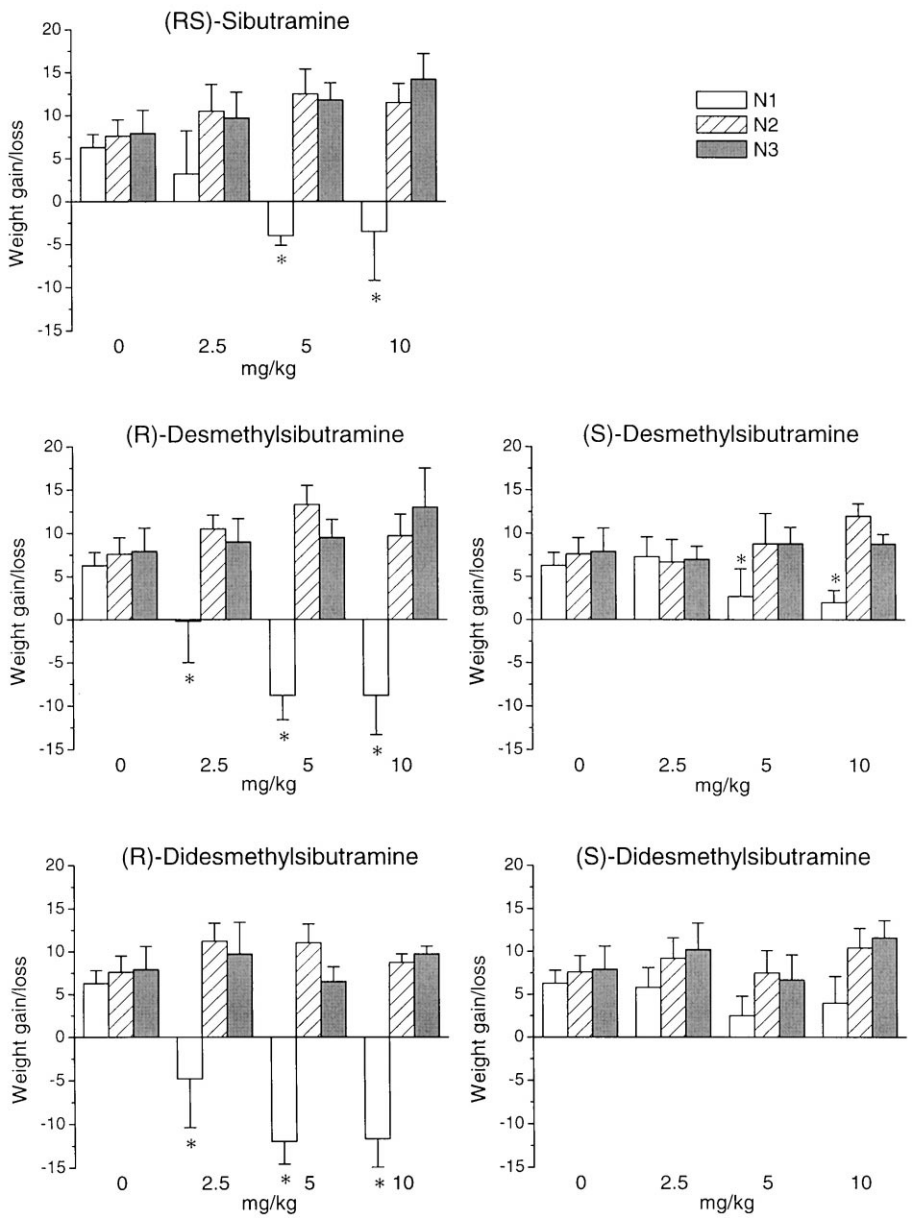

Fig. 3. Treatment (all $N = 6$/group; means ± S.E.M.) effects on body weight in terms of changes over each nightly (4:00 p.m.–10:00 a.m.) test period (N1, N2 and N3 refer to first, second and third nights after drug administration, respectively); * [drug vs. vehicle] indicate significant differences ($P < 0.05$, Newman–Keuls post-hoc tests).

ment effects on food and water consumption in terms of differences from baseline values (average of two nights preceding drug administration) and on body weight in terms of changes over each nightly test period.

On the night of administration, sibutramine had significant effects on food intake [ANOVA (analysis of variance), dose × time interaction: $F(6,44) = 8.90$, $P < 0.00001$; Newman–Keuls post-hoc tests, $P < 0.05$], water intake [ANOVA, dose × time interaction: $F(6,44) = 4.21$, $P < 0.002$; Newman–Keuls post-hoc tests, $P < 0.05$], and body weight [ANOVA, dose × time interaction: $F(6,44) = 6.74$, $P < 0.00001$; Newman–Keuls post-hoc tests, $P < 0.05$] at 5 and 10 mg/kg; the 10 mg/kg dosage also had a significant effect on food intake on the following night. On the night of administration, the (*R*) enantiomers of both desmethylsibutramine and didesmethylsibutramine significantly decreased food intake [ANOVAs, respectively, dose × time interaction: $F(6,44) = 25.40$ and 14.92, $P < 0.00001$; Newman–Keuls post-hoc tests, $P < 0.05$], water intake [ANOVAs, respectively, dose × time interaction: $F(6,44) = 5.20$ and 4.26, $P < 0.002$; Newman–Keuls post-hoc tests, $P < 0.05$], and body weight [ANOVAs, respectively, dose × time interaction: $F(6,44) = 12.15$ and 12.28, $P < 0.00001$; Newman–Keuls post-hoc tests, $P < 0.05$] at all doses (2.5, 5 and 10 mg/kg). In addition, (*R*)-desmethylsibutramine, at 10 mg/kg, significantly decreased water intake on the following night and (*R*)-didesmethylsibutramine, at 5 and 10 mg/kg, significantly decreased both food and water intake on the following night. While the (*S*)-enantiomer of didesmethylsibutramine had no significant effects (ANOVAs, $P < 0.2$–0.9), (*S*)-desmethylsibutramine had overall significant effects on food intake [ANOVA, dose × time interaction: $F(6,44) = 6.56$, $P < 0.0001$], water intake [ANOVA, dose × time interaction: $F(6,44) = 2.61$, $P < 0.03$], and body weight [ANOVA, dose × time interaction: $F(6,44) = 4.71$, $P < 0.001$] on the night of administration; Newman–Keuls post-hoc tests showed significant ($P < 0.05$) effects on food intake at 10 mg/kg and on body weight at 5 and 10 mg/kg.

In subsequent analyses, the effects of 10 mg/kg of the (*R*)- and (*S*)-enantiomers were compared to each other

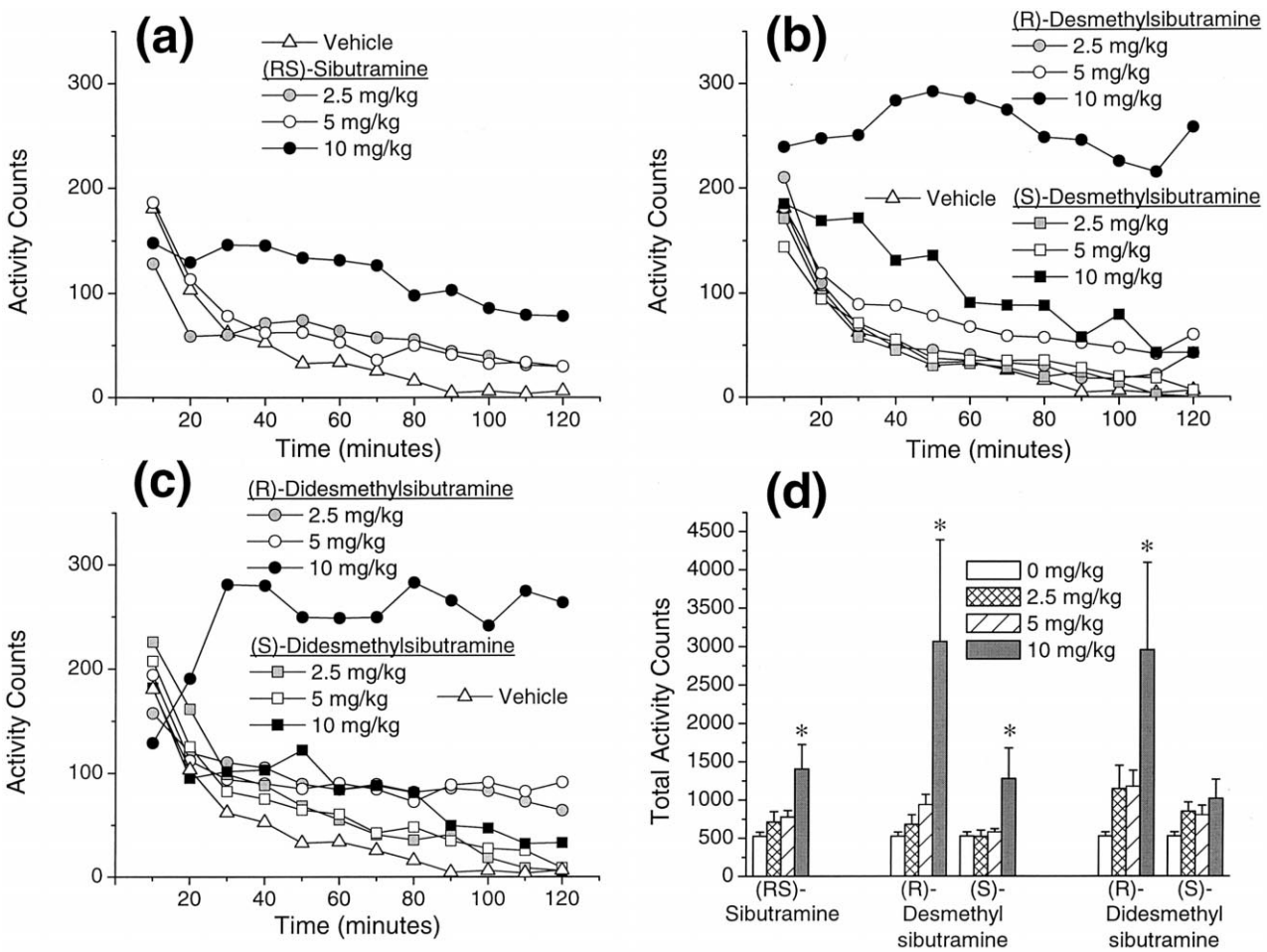

Fig. 4. Treatment effects on locomotor activity measured for two hs after drug administration ($N = 5$–11/group; means ± S.E.M.). Although there were significant time-dependent effects of all drugs, the (*R*)-enantiomers had significantly greater effects than their respective (*S*)-enantiomers and than sibutramine; refer to text for details of statistical analysis of time-course data (a–c). For total activity (d), ANOVA's were also significant for all drugs ($P < 0.03$–0.002); * [drug vs. vehicle] indicate significant effects of individual doses in total activity ($P < 0.05$, Newman–Keuls post-hoc tests).

and to the effects of sibutramine. For food intake, the effects of both (*R*)-enantiomers were significantly greater than their respective (*S*)-enantiomers on both nights and greater than sibutramine on the first night [ANOVA, $F(10,54) = 13.93$, $P < 0.00001$; Newman–Keuls post-hoc tests, $P < 0.05$]. The effects of the (*R*)-enantiomers were similar on water intake although only the effect of (*R*)-didesmethylsibutramine was significantly greater than that of sibutramine on the first night [ANOVA, treatment × drug interaction: $F(10,54) = 3.63$, $P < 0.001$; Newman–Keuls post-hoc tests, $P < 0.05$]. On body weight loss, the effects of (*R*)-desmethylsibutramine and (*R*)-didesmethylsibutramine were each significantly greater than that of sibutramine during the first night; there were no differences among any groups on subsequent nights indicating that the initial weight losses produced by the active drugs were maintained, there being no evidence of any subsequent compensation.

3.3. Effects on locomotor activity

Fig. 4(a–d) shows treatment effects on locomotor activity measured for two h after drug administration. With reference to Fig. 4(a), an ANOVA showed significant effects of sibutramine that varied with dose and time [dose effect, $F(3,34) = 4.92$, $P < 0.006$; time effect, $F(11,374 = 32.86$, $P < 0.0001$; interaction, $F(33,374) = 3.14$, $P < 0.00001$]; Newman–Keuls post-hoc tests showed significant effects ($P < 0.01$) of 10 mg/kg from 30 to 120 min after administration.

Analysis (ANOVA) of the data in Fig. 4(b) showed that the effects of (*R*)- and (*S*)-desmethylsibutramine also varied with dose and time [dose, $F(2,30) = 5.72$, $P < 0.008$; time, $F(11,330) = 25.05$, $P < 0.0001$; interaction, $F(22,330) = 2.30$, $P < 0.0009$]; the overall difference between (*R*)- and (*S*)-desmethylsibutramine was of marginal significance [$F(1,30) = 3.59$, $P < 0.06$] although Newman–Keuls post-hoc tests showed significant ($P < 0.00005$) differences between the effects of the 10 mg/kg doses from 40 to 120 min after administration. Subsequent ANOVAs separately comparing each of the enantiomers to vehicle showed significant effects of both (*R*)-desmethylsibutramine [dose, $F(3,30) = 6.51$, $P < 0.002$; time, $F(11,330) = 21.6$, $P < 0.001$, interaction, $F(33,330) = 2.73$, $P < 0.00001$] and (*S*)-desmethylsibutramine [dose, $F(3,24) = 4.81$, $P < 0.01$; time, $F(11,264) = 75.45$, $P < 0.0001$; interaction, $F(33,264) = 2.06$, $P < 0.001$]. Newman–Keuls post-hoc tests showed significant ($P < 0.00001$) effects of the 10 mg/kg dose of (*R*)-desmethylsibutramine from 20 to 120 min after administration and significant ($P < 0.02$) effects of the 10 mg/kg dose of (*S*)-desmethylsibutramine from 20 to 80 and again at 100 min after administration.

Analysis (ANOVA) of the data in Fig. 4(c) showed an overall significant difference [$F(1,29) = 5.35$, $P < 0.03$) between the effects of (*R*)- and (*S*)-didesmethylsibutramine as well as variation with dose and time [dose, $F(2,29) = 3.01$, $P < 0.06$; time, $F(11,319) = 14.03$, $P < 0.00001$; interaction, $F(22,319) = 4.19$, $P < 0.00001$]. Newman–Keuls post-hoc tests showed significant ($P < 0.0001$) differences between the effects of the 10 mg/kg doses from 20 to 120 min after administration. Subsequent ANOVAs separately comparing each of the enantiomers to vehicle showed significant effects of both (*R*)-dide-

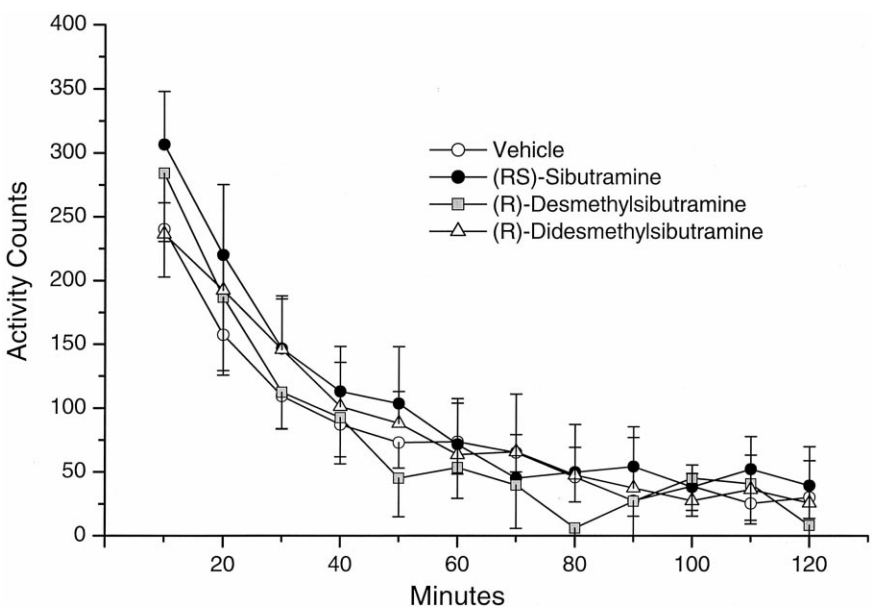

Fig. 5. Lack of treatment effects on locomotor activity measured 24–26 hs after drug administration (all doses 10 mg/kg; all $N = 6$/group; means ± S.E.M.).

smethylsibutramine [dose, $F(3,29) = 6.43$, $P < 0.002$; time, $F(11,319) = 4.88$, $P < 0.00001$, interaction, $F(33,319) = 6.45$, $P < 0.00001$] and (*S*)-desmethylsibutramine [dose, $F(3,24) = 3.69$, $P < 0.03$; time, $F(11,264) = 78.42$, $P < 0.0001$; interaction, $F(33,264) = 1.81$, $P < 0.006$]. Newman–Keuls post-hoc tests showed significant ($P < 0.04$–0.00001) effects of the 2.5, 5 and 10 mg/kg doses of (*R*)-didesmethylsibutramine from 90–100, 90–120 and 10–120 min after administration, respectively, and significant ($P < 0.04$) effects of the 10 mg/kg dose of (*S*)-didesmethylsibutramine at 50, 70 and 80 min after administration.

Analysis (ANOVA) of treatment effects on total activity, shown in Fig. 4(d), also showed significant differences among drugs and doses [drug, $F(4,81) = 3.16$, $P < 0.02$; dose, $F(2,81) = 11.54$, $P < 0.00001$]. Newman–Keuls post-hoc tests confirmed the significant ($P < 0.02$) differences between the 10 mg/kg effects of the (*R*)- and (*S*)-enantiomers of each metabolite. Furthermore, at 10 mg/kg, the effects of (*R*)-desmethylsibutramine and (*R*)-didesmethylsibutramine were each significantly ($P < 0.02$) greater than the effect of sibutramine.

Because the 10 mg/kg doses of (*R*)-desmethylsibutramine and (*R*)-didesmethylsibutramine as well as sibu-

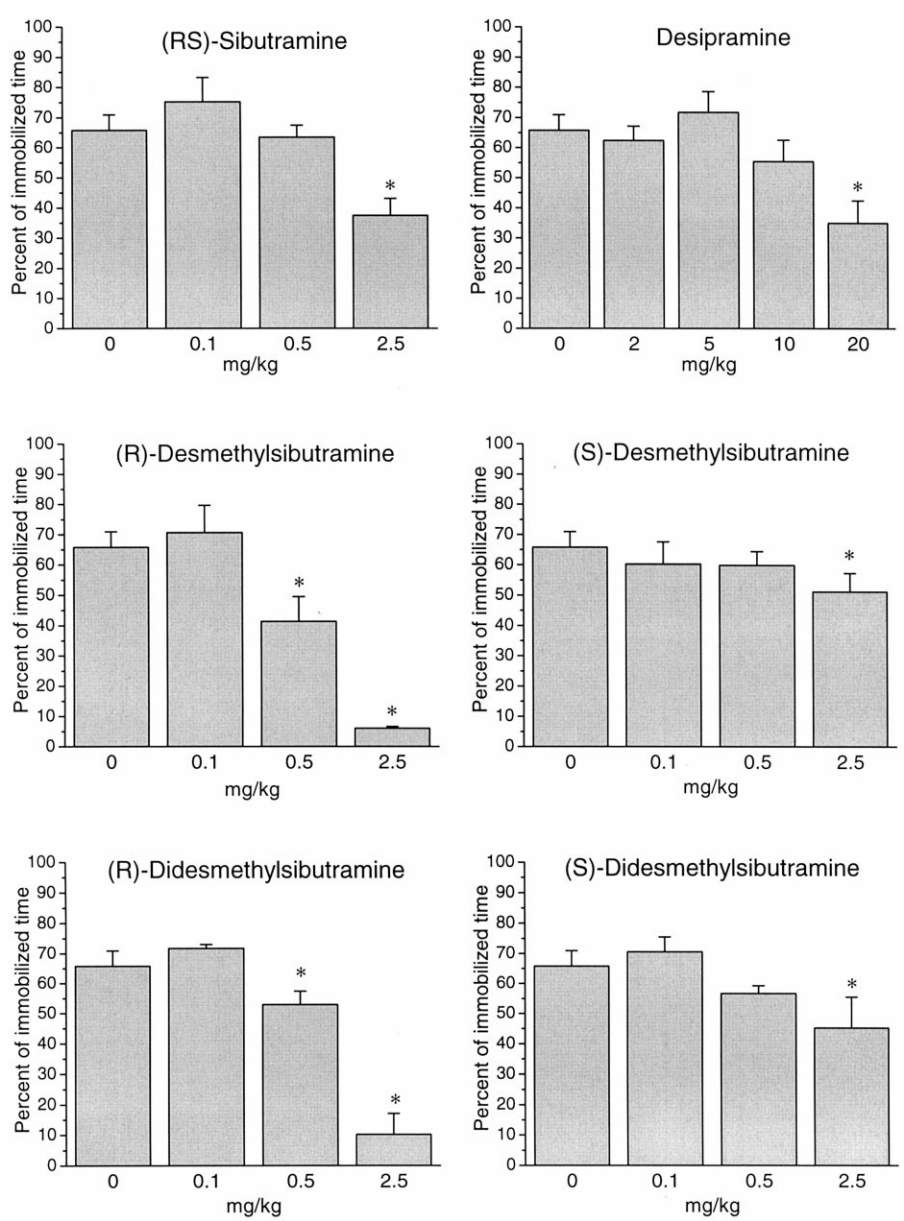

Fig. 6. Treatment effects on the Porsolt test ($N = 5$–17/group; means ± S.E.M.; see text for procedure). Although there were significant effects of all drugs, the (*R*)-enantiomers had significantly greater effects than their respective (*S*)-enantiomers and than sibutramine; * [drug vs. vehicle] indicate significant differences ($P < 0.05$, Newman–Keuls post-hoc tests).

tramine still appeared to induce hyperactivity at two h after administration, other groups of rats were treated with 10 mg/kg doses of these agents 24 h prior to testing. As shown in Fig. 5, there were no significant effects of any drug at that time.

3.4. Effects on ''behavioral despair'' (Porsolt swim test)

Fig. 6 shows treatment effects on in the Porsolt swim test in terms of the percent of immobilized time. Desipramine, which was used as a positive control, had a significant effect at 20 mg/kg [ANOVA, $F(4,33) = 12.32$, $P < 0.00001$; Newman–Keuls post-hoc tests, $P < 0.05$]. Sibutramine and both enantiomers of both metabolites all had significant effects at 2.5 mg/kg (ANOVAs, $P < 0.04$–0.00001; Newman–Keuls post-hoc tests, $P < 0.05$); however, only (*R*)-desmethylsibutramine and (*R*)-didesmethylsibutramine had significant effects at 0.5 mg/kg (Newman–Keuls post-hoc tests, $P < 0.05$).

4. Discussion

The present results show that both desmethylsibutramine and didesmethylsibutramine are enantioselective: the (*R*)-enantiomers were clearly more potent than the (*S*)-enantiomers. Furthermore, both (*R*)-desmethylsibutramine and (*R*)-didesmethylsibutramine were more potent than sibutramine. While (*S*)-desmethylsibutramine had some effect on all tests, (*S*)-didesmethylsibutramine affected locomotor behavior and the Porsolt test but appeared to be completely inactive on food intake. This suggested a dissociation between the effects of the metabolites on consummatory behavior versus their effects on arousal and/or affective state. The distinction was confirmed by the fact that (*R*)-desmethylsibutramine, (*R*)-didesmethylsibutramine and sibutramine all decreased food intake during the second night after administration (from 24 to 42 h post-treatment) of 10 mg/kg while none of these agents affected locomotor activity when tested a day after (from 24 to 26 h) the same treatments. Furthermore, (*R*)-desmethylsibutramine influenced consummatory and Porsolt test behaviors at doses (2.5 and 5 mg/kg) that were ineffective, even in the first 2 h, on locomotor activity.

The observations that sibutramine and its active metabolites stimulated locomotor activity are consistent with other in vivo (Martin et al., 1995) and in vitro (Luscombe et al., 1989; Heal et al., 1998) data indicating that these agents have dopamimetic effects. However, the observation that food intake can be suppressed in the absence of locomotor stimulation is also consistent with other findings (Heal et al., 1992; Jackson et al., 1997a,b) suggesting that the dopaminergic action of sibutramine is not essential for its anorectic effect. Although the latter may be the case, a dopaminergic action is still likely to have a role in mediating potential side effects of sibutramine at high doses.

The relative selectivity of sibutramine and its metabolites for inhibiting in vitro uptake of norepinephrine and dopamine versus serotonin (Table 1) is consistent with previously published data (Luscombe et al., 1989). One perplexing aspect of the present data is the fact that (*S*)-didesmethylsibutramine was almost as potent an inhibitor of norepinephrine and dopamine uptake as (*R*)-didesmethylsibutramine yet clearly much less potent in all behavioral assays. This might suggest that the serotonin effects of these drugs are the most important, since (*R*)-desmethylsibutramine and (*R*)-didesmethylsibutramine were both much more potent (200 and 40 times, respectively) on serotonin uptake than their (*S*)-enantiomers. Alternatively, it is possible that the (*R*)- and (*S*)-enantiomers might be metabolized differently such that (*S*)-didesmethylsibutramine is inactivated much quicker than (*R*)-didesmethylsibutramine. In this regard, it is of interest to note that sibutramine and its metabolites were reported to inhibit norepinephrine, dopamine and serotonin uptake in vivo in rats with considerably different relative potencies than those observed in vitro (Luscombe et al., 1989). Data from humans are also confusing. Just the reverse of what has been found in rats, it is has been claimed that, in human brain, sibutramine has a tenfold selectivity in vitro for inhibiting serotonin versus norepinephrine uptake (Heal et al., 1998). However, the only published human data appeared in a review article (Heal et al., 1998) in which no methodological details (e.g., number of brains studied, assay conditions etc.) or indices of variance (e.g., S.E.M.) were given. Furthermore, another study (Luscombe et al., 1990), in which plasma samples from persons administered sibutramine were assayed for monoamine uptake, concluded that the relative potencies of sibutramine to inhibit reuptake of norepineprhine, dopamine and serotonin were similar to those reported in rats.

While it is generally believed (e.g., Luscombe et al., 1989; Heal et al., 1998) that the efficacy of sibutramine in the treatment of obesity is largely or entirely attributable to the actions of desmethylsibutramine and didesmethylsibutramine, it is not clear if the hypertensive and other side effects of sibutramine are also mediated by the same metabolites or in part by sibutramine itself. It is also possible that the (*S*)-enantiomers of desmethylsibutramine and didesmethylsibutramine may, to some extent, contribute to sibutramine's side effect profile. The present results, showing that the (*R*)-enantiomers are more potent than sibutramine in depressing food intake and decreasing body weight, suggest that these enantioselective metabolites might be safer and more effective than sibutramine as potential therapies for obesity.

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