Effect of salidroside, active principle of *Rhodiola rosea* extract, on binge eating

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**ABSTRACT**

Stress is a key determinant of binge eating (BE). Since *Rhodiola rosea* is known to modulate stress responses, its effect in a model of BE was investigated. BE for highly palatable food (HPF) was evoked in female rats by three 8-day cycles of food restriction/refeeding (for 4 days 66% of the usual chow intake; for 4 days food ad libitum) and acute stress on the test day (day 25). *R. rosea* dry extract (3% rosavin, 3.12% salidroside) or its active principles were given by gavage 1 h before access to HPF. Only rats exposed to both food restrictions and stress exhibited BE in the first 15–60 min after the stressful procedure. *R. rosea* extract 10 mg/kg significantly reduced and 20 mg/kg abolished the BE episode. *R. rosea* extract 20 mg/kg abolished also stress-induced increase in serum corticosterone levels. The *R. rosea* active principle salidroside, but not rosavin, at doses present in the extract, dose-dependently reduced or abolished BE for the period in which it was elicited.

In conclusion results indicate that *R. rosea* extracts may have therapeutic properties in bingeing-related eating disorders and that salidroside is the active principle responsible for this effect.

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1. Introduction

Episodes of binge eating (BE) in humans are characterized by compulsive, non-homeostatic consumption of an unusually large quantity of highly palatable food (HPF) in a short period of time. Even though not hungry, subjects eat more rapidly than normal until feeling uncomfortably full. These episodes are accompanied by subjective sense of loss of control over eating, and are associated with feeling of distress, disgust, depression, being guilty about overeating and eating alone because of embarrassment [1].

BE represents a central feature of bulimia nervosa, in which episodes of BE are followed by behaviors aimed at avoiding weight gain, such as self-induced vomiting. Intense and persistent BE episodes represent a typical phenomenon occurring also in subjects suffering from binge eating disorder (BED) [2]. The BED, described for the first time by A.J. Stunkard [3], is probably the most prevalent eating disorder [4]. It is characterized by repeated episodes of BE in the absence of compensatory behaviors to avoid weight gain. The DMS-IV-TR [1] indicates among diagnostic criteria for BED that BE episodes should occur at least 2 days per week for 6 months. The BED is associated with significant medical and psychiatric co-morbidity [5–7]. It is estimated that BE afflicts approximately 5% of the US adult population at some time in their life [8], and it contributes to aggravate obesity and associated pathologies [4,9–11].

A large body of evidence suggests that dieting, stress and negative affective states represent possible triggers of BE in patients suffering from BED or bulimia nervosa [12,13]. Indeed, dieting periods are a common finding in the history of binge eaters, although hunger per se appears to be not enough to induce BE in the absence of stress and negative affective state [14,15]. Considerable evidence suggests that BE may be caused by a unique interaction between dieting and stress; thus, environmental stress and a history of cyclic food restrictions may be responsible for its precipitation and maintenance [16–18]. Accordingly, recurring food restrictions are consistently the strongest predictor of overeating in response to stress [12].

Despite a growing recognition of the consequences of bulimia nervosa and of BED on public health, satisfactory treatments are not available at present [19]. Fluoxetine has been approved by the FDA for bulimia nervosa, but evidence for its efficacy is reported inconclusive [20]. Apparently, treatment of BED and bulimia nervosa cannot simply rely on pharmacological agents aimed at reducing food intake in general, like serotonergic drugs. BE episodes appear to be characterized by uncontrollable urge to obtain and consume food, which is similar to that exhibited by addicted individuals towards drug abuse. In this regard it is interesting to note that several drugs that influence alcohol addiction (such as naltrexone, baclofen and topiramate), have been reported to reduce BE in experimental models [21–24].

Medications that at present have been suggested to reduce BE in clinical studies, like topiramate [25,26] or sibutramine [27,28] are...
associated with a variety of adverse side effects, which represent a serious problem during chronic treatment [29–31]; in particular sibutramine has been recently withdrawn from the European market. Innovative treatments for bulimia nervosa and BED, devoid of severe side effects, are strongly needed.

Therefore, the present study was aimed at investigating the effect of intragastric administration of a dry extract of *Rhodiola rosea* L. (fam. Crassulaceae), as well as of its active principles salidroside and rosavin, in a model of BE in female rats. *R. rosea* is a plant commonly used in traditional medicine in Eastern Europe and Asia for its "adaptogenic" properties, that is for its ability to increase body resistance to physical, chemical or biological stressors in experimental animals and in humans [32,33]. The anti-stress properties have been attributed to modulation of the activity of the sympathetic-adrenal system and of the hypothalamic-pituitary-adrenal axis, as well as to influence on key mediators of the stress response such as molecular chaperons like Hsp70, stress-activated c-Jun N-terminal protein kinase (JNK1), Forkhead Box O transcription factor DAF-16, cortisol and nitric oxide [33–35]. Moreover, *R. rosea* extracts have been reported to reduce also behavioral responses evoked by central CRF administration, such as CRF-induced anorexia [36].

Since stress is considered a key determinant of BE, it was considered interesting to evaluate the effect of *R. rosea* extracts in an experimental model of BE [24], derived with modifications from the method of Hagan et al. [37], in which BE is evoked by combining stress and repeated episodes of food restriction.

It is well known that *R. rosea* roots contain a variety of biologically active compounds, including organic acids, flavonoids, tannins and phenolic compounds. Phenylpropane and phenylethanoid phenolic glucosides, such as salidroside, rosavin, syringin and triandrin are considered the most important active principles [33]. In particular, extracts of *R. rosea* are usually standardized for rosavin and salidroside [38]; therefore, the effect on BE of purified rosavin and salidroside were also evaluated in the present study.

2. Experimental procedures

A preclinical model has been recently developed by our group to investigate the neuro- and psychobiology of BE, and to identify innovative pharmacological treatments [24]. The model employs female rats in relation to the higher prevalence of binge-type eating disorders in women than in men [1,4].

This model [24] combines three 8-day cycles of food restriction/re-feeding and acute stress (on the 25th day) to evoke BE for sweet highly palatable food (HPF) in Sprague–Dawley female rats. It represents an evolution of the model of Hagan et al. [37], the main difference from the latter being the stressful procedure adopted.

2.1. Animals

Female Sprague–Dawley rats (Charles River, Calco, Como, Italy) were employed. Their body weight was 225–250 g at the beginning of the experiments. Rats were acclimated to individual cages under a 12-h light/dark cycle (lights on at 08:00 h) with *ad libitum* chow and water for 2 weeks prior to the experiments. They were kept in a room at constant temperature (20–22 °C) and humidity (45–55%).

Rats were kept in individual cages with metallic walls; the floor and the front wall were made of metallic grid. The dimensions of the cage floor were 30 cm × 30 cm; the cage was 30 cm high. A front door (30 cm × 20 cm) made of metallic grid was present in the anterior wall of the cage to get access to the inside of the cage; the remaining part of the front wall was equipped with a drinking burette. All the procedures were conducted in adherence with the European Community Council Directive for Care and Use of Laboratory Animals.

2.2. Diet

Animals were offered standard rat food pellets, 4RF18, Mucedola, Settimo Milanese, Italy (2.6 kcal/g). The HPF was a paste in texture, prepared by mixing Nutella (Ferrero, Alba, Torino, Italy) chocolate cream (5.33 kcal/g; 56%, 31% and 7% from carbohydrate, fat and protein, respectively), grounded food pellets 4RF18, Mucedola, Settimo Milanese, Italy and water in the following weight/weight percent ratio: 52% Nutella, 33% food pellets, and 15% water. The HPF diet had a caloric content of 3.63 kcal/g.

Standard pellets were offered inside a metallic grid container that was hung on the anterior wall of the cage; it was removed from the cage to measure its weight in order to determine food pellet intake. HPF was offered in a coffee cup; the handle of the cup was inserted into the metallic grid of the anterior wall of the cage and fixed to the wall by means of a small plastic stick.

2.3. The stressful procedure

For 15 min the china coffee cup containing HPF was placed inside a metallic grid container that was hanged up on the anterior wall of the cage. In these conditions the animal was able to see the cup in which it received HPF on days 5, 6, 13 and 14 of the first two cycles, was able to see the HPF itself and to smell its odor. In this 15 min period the rat engaged in repeated movements of the forepaws, head and trunk aimed at obtaining the HPF, but it was not able to reach it. This expedient was adopted to generate a mild stressful condition characterized by temporary lack of control over the environmental circumstances; it causes a significant increase in serum corticosterone levels [24]. Rats underwent the stressful procedure between 10:00 and 12:00 h. After 15 min, the cup was placed inside the cage of rats of the stress groups, so that HPF became accessible to them.

2.4. Drug treatment

*R. rosea* dry extract containing 3% rosavin and 3.12% salidroside (Arda Natura, Piacenza, Italy) was dissolved in 2% ethanol and water and administered by gavage 1 h before access to HPF at doses of 10 or 20 mg/kg. Salidroside and rosavin were purchased from Chengdu Biopurify Phytochemicals Ltd. (Chengdu, Sichuan, China). Like the extract, they were dissolved in 2% ethanol and water and administered by gavage 1 h before access to HPF at doses of 312–936 μg/kg for salidroside and of 600 μg/kg for rosavin. Control rats received vehicle administration by gavage.

2.5. Experiment 1. Effect of *R. rosea* extract on BE evoked by cycles of food restriction and exposure to acute stress

One hundred and twenty female rats were employed. They were divided in 4 groups of 30 animals, matched for body weight and daily food intake: 1) the non-restricted and not exposed to stress group (NR + NS), 2) the restricted and not exposed to stress group (R + NS), 3) the non-restricted and exposed to stress group (NR + S), and 4) the restricted and exposed to stress group (R + S).

Rats were submitted to 3 consecutive 8-day cycles followed by the final test on day 25 [24,37]. Each 8-day cycle was as follows: a) the control group (NR + NS) had chow *ad libitum* for 4 days, on days 5–6 they received chow *ad libitum* + HPF for 2 h (from 10:00 a.m., that is 2 h after the beginning of the light phase of the cycle); on days 7–8 they had chow *ad libitum*; on day 25 they were not exposed to stress; b) the second group (R + NS) had chow restricted to 66% of the usual intake for 4 days, was offered chow *ad libitum* and HPF for 2 h on days 5–6 and only chow on days 7–8; on day 25 they were not exposed to stress. In the first cycle, the 66% of food offered was calculated on the basis of the mean intake of each group in the 4 days preceding the beginning of the experiment. For the following
two 8-day cycles, the 66% was calculated on the basis of the mean intake of each group during the last day of the previous 8-day cycle; c) the third group had Chow and HPF as controls, but on the test day (day 25) it was exposed to stress (NR + S); d) the fourth group (R + S) had food available like group b) and on day 25 it was exposed to stress.

The 8-day cycle was repeated three times, but in the third cycle the animal did not have access to HPF on days 21 and 22, in order to avoid that access to HPF shortly before day 25 might have reduced motivation for it in the final test. On day 25, free access to HPF and Chow was offered and their intake was measured in the first 2 h taking care to collect any spillage.

It has been recently reported by our group that in the estrous phase of the ovarian cycle female rats do not exhibit BE without significant differences in intensity. Therefore, immediately after the test on day 25 vaginal smears were collected and analyzed under microscope to assess the ovarian phase, and data from rats in the estrous phase were not included in the statistical analysis. Vaginal smears were analyzed by an experienced experimenter blind to treatment conditions.

Each group of 30 rats was divided in 3 subgroups, treated respectively with vehicle, R. rosea dry extract, 10 or 20 mg/kg, given by gavage 1 h before access to HPF. Food intake was expressed as mean kcal/kg ingested ± S.E.M.; it was measured for 2 h, since previous experiments showed no differences between groups after this period. HPF intake was measured at 15, 30, 60, and 120 min after access to it. Food pellet intake was measured only at 2 h, in relation to the findings of previous studies showing that the food pellet intake was very small, and to avoid disturbance to the animals during the test [24].

2.6. Experiment 2. Effect of R. rosea extract on serum corticosterone levels following cycles of food restriction and exposure to acute stress

Additional thirty-two Sprague-Dawley rats, divided in two groups (NR + NS and R + S) of 16 animals, were subjected to 3 cycles of 8 days with the same procedure described under Experiment 1: a) the control group (NR + NS) had Chow ad libitum for 4 days, on days 5–6 they received Chow ad libitum + HPF for 2 h; on days 7–8 they had Chow ad libitum; on day 25 they were not exposed to stress; b) the second group (R + S) had Chow restricted to 66% of the usual intake for 4 days, was offered Chow ad libitum and HPF for 2 h on days 5–6 and only Chow on days 7–8; on day 25 they were exposed to stress. Again, on days 21 and 22 they did not have access to HPF. At the end of the third cycle (on day 25) 8 animals in each group received vehicle by gavage, while the other 8 received R. rosea dry extract, 20 mg/kg, by gavage. The R + S group received the administration by gavage 45 min before exposure to the stressful procedure and was sacrificed at the end of the 15 min period of stress. In the NR + NS group 8 animals received vehicle by gavage, while the other 8 received R. rosea dry extract, 20 mg/kg, by gavage. They were sacrificed 60 min after the gavage administration.

Blood samples were collected from the trunk after rat decapitation. To improve serum separation from whole blood, samples were allowed to clot at room temperature before centrifugation (1000 × g for 10 min). Serum was transferred into clean tubes and stored at −20 °C until the assay. Taking into account the circadian rhythm of corticosterone, all sacrifices were carried out between 12:00 a.m. and 2:00 p.m., i.e. during the diurnal period when its concentrations are relatively constant [40,41]. Assessment of serum corticosterone level was done by means of enzyme immunoassay (EIA) using a commercially available kit (Assay Design Inc, Ann Arbor, MI, USA), which utilizes microplate reader set at 405 nm. Serum samples were diluted 1:20 in appropriate assay buffer in order to be within the calibration curve range and assayed in duplicate. The detection limit of the assay was 26.7 pg/ml; intra- and inter-assay coefficients of variations were, respectively, 7.4 and 9.1%.

2.7. Experiment 3. Effect of R. rosea extract on food intake in non-cycled food sated or deprived rats

This experiment was carried out to later rule out drug’s effect on homeostatic mechanisms of feeding. A separate group of eighteen female rats, with food pellets available ad libitum, was divided in 3 subgroups of 6 rats. At 10:00 a.m. they received administration by gavage of R. rosea extract, 10 or 20 mg/kg, or vehicle (controls) and were temporarily placed in their individual cage without food. One hour after the intra gastric administration rats were offered again food pellets (4RF18, Mucedola) and their food and water intake was measured for 2 h.

A week later, the same 18 female rats were deprived of food, but not of water for 16 h. Afterwards, they were divided in 3 groups of 6 rats, counterbalanced for drug treatment in regard to the previous experiment. At 10:00 a.m. they received administration by gavage of R. rosea extract, 10 or 20 mg/kg, or vehicle (controls) and were temporarily placed in their individual cage without food. One hour after intra gastric administration rats were offered again food pellets (4RF18, Mucedola) and their food and water intake was measured for 2 h.

2.8. Experiment 4. Effect of rosavin and salidroside on BE evoked by cycles of food restriction and exposure to acute stress

Additional fifty-four female rats, divided in 2 groups (NR + NS and R + S) of 27 rats, were submitted to the same experimental procedure as in Experiment 1. Only two groups of rats were used in the present experiment since both NR + S and R + NS rats do not develop BE and only served as a control to fully characterize the effect of R. rosea on HPF intake. On the test day (day 25), 1 h before access to HPF, either vehicle or rosavin or salidroside (at doses, respectively, of 600 or 624 μg/kg, i.e. the same amounts contained in 20 mg/kg of the dry extract) were given by gavage.

Since salidroside evoked a statistically significant effect, an additional group of rats was employed to evaluate the dose-response relationship for its effect. Forty five female rats were employed, divided in the 5 groups of 9 rats each, which were treated as follows on the test day (day 25) 1 h before access to HPF: Group 1 (NR + NS) was treated with vehicle, Group 2 (R + S) was treated with vehicle, Group 3 (R + S) received salidroside 312 μg/kg, Group 4 (R + S) received salidroside 624 μg/kg, Group 5 (R + S) was treated with salidroside 936 μg/kg.

After exposure to stress, free access to HPF and Chow was offered and their intake was measured in the first 2 h taking care to collect any spillage. Food intake was expressed as mean kcal/kg ingested ± S.E.M.

2.9. Statistical analysis

Results are expressed as means ± S.E.M. Data were analyzed by two ways analysis of variance with between subject comparisons for experimental groups or drug treatments, and within subject comparison for time of observation. Post-hoc comparisons were carried out by the Bonferroni test. Statistical significance was set at P < 0.05.

3. Results

3.1. Experiment 1. Effect of R. rosea on BE evoked by cycles of food restriction and exposure to acute stress

Eighty seven female rats (of the 120 employed in the experiment) proved not to be in the estrous phase at the moment in which the
experiment was carried out. Only data from these animals (6–8 per group) were submitted to statistical analysis.

As shown in Fig. 1, body weight of rats was reduced during the 4 days of food restriction, but immediately afterwards the animals increased their food intake and rapidly recovered their body weight to levels of controls by the end of each cycle. On the test day body weight of the 4 groups of animals, as well as their food intake in the previous 24 h were not significantly different.

The ANOVA revealed a highly significant difference in 2-h HPF intake in the 4 groups of rats following vehicle administration \[F(3,26) = 14.3; P < 0.01\]. As shown in Fig. 2, following vehicle administration HPF intake in the R+S group was markedly higher than that of the control (NR+NS) group. HPF intake of R+S rats was very pronounced in the first 15 min of access to it; these animals never engaged in competing behaviors, but continuously remained over the cup containing HPF and focused their attention on the intake.

Cumulative HPF intake in the R+S group was significantly higher than in controls up to 60 min after access to it. HPF intake of the NR+S group was not significantly different from that of controls (NR+NS), indicating that cycles of food restriction/re-feeding. Data on days 5, 6 and 13, 14 include both chow and HPF intake. Values are means±S.E.M.

Fig. 1. In Panel A, body weight of female rats during the three 8-day cycles of food restriction/re-feeding. In Panel B, food intake of female rats during the three 8-day cycles of food restriction/re-feeding. Data on days 5, 6 and 13, 14 include both chow and HPF intake. Values are means±S.E.M.

The intake of standard food pellet, was very small (about 3–5% of the overall calories intake in the 2-h test) and it was affected neither by food restriction, nor by stress, nor by the combination of both. In the 2-h test, rats of the R+S group ate 191.8 kcal/rat of HPF and only 7.3 kcal/rat of food pellets.

As shown in Fig. 2, R. rosea extract significantly reduced HPF intake in the R+S group \[F(2,21) = 4.49; P<0.05\], but not in the other groups: NR+NS \[F(2,21) = 0.67; P>0.05\]; R+NS \[F(2,17) = 0.22; P>0.05\]; NR+S \[F(2,16) = 0.53; P>0.05\] in the absence of drug treatment–time interaction. Post-hoc comparisons revealed that the effect of R. rosea in the R+S group was statistically significant at 15 and 60 min in response to 10 mg/kg, and at 15, 30 and 60 min following administration of 20 mg/kg, that is for the whole period in which BE was exhibited. HPF intake at 120 min after access to it was still lower than in controls, but the difference was not statistically significant following both doses.

3.2. Experiment 2. Effect of R. rosea extract on serum corticosterone levels following cycles of food restriction and exposure to acute stress

Two-way ANOVA showed significant group effect \[F(1,28) = 13.9, P<0.01\], drug treatment effect \[F(1,28) = 19.6, P<0.01\] and group–drug interaction \[F(1,28) = 8.93, P<0.01\] on serum corticosterone levels. As reported in Fig. 3, exposure to HPF without access to it increased corticosterone levels in the serum samples obtained from R+S rats, sacrificed 15 min after the beginning of the stressful procedure in comparison to NR+NS rats.

The administration by gavage of R. rosea extract at the dose of 20 mg/kg completely abolished the increase in serum corticosterone levels in the R+S group. Post-hoc comparisons revealed that serum corticosterone levels in R+S rats treated with R. rosea extract were not significantly different from those of NR+NS rats, either treated or not with R. rosea.

3.3. Experiment 3. Effect of R. rosea extract on food intake in non-cycled food sated or deprived rats

R. rosea extract, 10 or 20 mg/kg, did not significantly modify food pellet intake in sated rats \[F(2,15) = 2.99; P>0.05\] or in 16-h food deprived animals \[F(2,15) = 0.28; P>0.05\] (data not shown).

3.4. Experiment 4. Effect of rosavin or salidroside on BE evoked by cycles of food restriction and exposure to acute stress

As shown in Fig. 4A, salidroside, 624 μg/kg, administered by gavage 1 h before access to HPF significantly reduced the increase in HPF intake in R+S rats \[F(1,13) = 5.03; P<0.05\]. On the other hand, it did not significantly modify HPF intake in NR+NS rats.

As shown in Fig. 4B, rosavin, 600 μg/kg, administered by gavage 1 h before access to HPF, slightly reduced HPF intake in R+S rats, however the difference from R+S rats receiving vehicle administration was not statistically significant \[F(1,14) = 3.0; P>0.05\]. Moreover, rosavin did not significantly modify HPF intake in NR+NS rats.

When salidroside was tested at doses ranging from 312 to 936 μg/kg the overall ANOVA revealed a statistically significant treatment effect \[F(3,27) = 3.77; P<0.05\]. The intake of HPF in R+S rats treated with vehicle was significantly different from that of NR+NS rats treated with vehicle only in the first 15 min. The intake of HPF in R+S rats treated with salidroside was significantly reduced in comparison to that of R+S rats treated with vehicle in response to all the doses tested. In response to 624 and 936 μg/kg the effect of salidroside was statistically highly significant (p<0.01) at 15 and 30 min after access to HPF, thus covering the whole time interval in which the rats exhibited BE. Following salidroside treatment HPF intake was essentially back to that of NR+NS rats (Fig. 5).
4. Discussion

The present study confirmed that stress or repeated food restrictions, given separately, are not enough to induce BE, but the combination of both determinants is required. The model has been shown to possess, in addition to face and construct validity, also predictive validity since both topiramate and sibutramine are able to abolish BE in this model[24].

The administration by gavage of a dry extract of *R. rosea*, 10 mg/kg, significantly reduced the increase in HPF intake in the R+S group (submitted to both stress and repeated food restrictions), while 20 mg/kg completely abolished it in the 1 h binge period. It is interesting to note that the daily doses of *R. rosea* recommended in humans are in the order of hundreds of mg/person/day[42], taken in 2–3 administrations/day; thus, the effective doses used in the present study prove to be in the same range of those recommended in humans.

While suppressing the increase in HPF intake in the R+S group, 20 mg/kg of *R. rosea* extract did not reduce HPF intake neither in the control group (NR+NS), nor in the NR+S group, nor in the R+NS group; moreover it did not modify the intake of food pellets in food sated or food deprived rats. Thus, the effect of *R. rosea* is not the expression of a general effect on food intake (like that evoked by serotonergic drugs, such as fluoxetine or sibutramine). In this regard the work of Cifani et al.[24] has shown that fluoxetine and sibutramine do not selectively reduce HPF intake in the R+S group, but reduce HPF intake in all the experimental groups (NR+NS, R+S, NR+S and R+NS). Fluoxetine and sibutramine exhibit effects different from that of *R. rosea* extract, suggesting that the effects of the latter are not mediated by serotonergic mechanisms.

The results of Experiment 2 show that *R. rosea* abolished the increase in serum corticosterone levels; since exposure to stress is necessary to evoke BE in the adopted model, it may be speculated that *R. rosea* abolishes BE by suppressing the activation of the HPA axis.

The anti-stress properties of *R. rosea* have been documented in humans and in experimental animals and have been attributed to interference both with HPA axis and the sympatho-adrenal system [33–35]. Evidence has been provided that *R. rosea* extract influence...
endogenous orexigenic compounds [43] may be important for the expression of the hyperphagic effect of BE for two reasons: on the one hand, corticosterone has been reported to increase peripheral β-endorphin levels [53], however, the possible involvement of these actions on the effects on BE and on serum corticosterone levels of *R. rosea* or its active principles remain to be investigated.

In addition to its effects on the stress system, *R. rosea* has been reported to influence catecholamines and serotonin by inhibiting MAO and COMT enzymes [51,52]; moreover, it has been reported to increase peripheral β-endorphin levels [53], however, the possible involvement of these actions on the effects on BE and on serum corticosterone levels of *R. rosea* or its active principles remain to be investigated.

While in the present study *R. rosea* extract inhibited BE, Mattioli and Perfumi [36] have shown that *R. rosea* antagonizes the anorectic effect of stress and of CRF; thus it increases food intake in conditions in which it was suppressed by stress or central CRF injection. Indeed, stress is well known to be responsible for both stimulation and inhibition of feeding [54,55], apparently depending on the intensity of the stress itself; mild stressors can stimulate feeding, while strong stressors, which result in high levels of CRF release in the brain, induce anorexia. Thus, the different effects evoked by *R. rosea* on feeding behavior, may likely be the consequence of its primary influence on the stress mechanisms [33,34], rather than a direct effect on orexigenic or anorexigenic mechanisms. By influencing the response to stress, *R. rosea* extracts can either suppress stress-induced BE or stress-induced anorexia. In the present study *R. rosea* extract did not modify the intake of HPF or of food pellets in NR+NS, R+NS, NR+S rats; moreover, it did not modify food intake in sated rats or in 16-h food deprived rats. These results provide clear evidence that the effect of *R. rosea* on food intake is not the expression of a direct interaction with the homeostatic hunger–satiety mechanisms controlling food intake.

The possible active principle(s) responsible for the effect of *R. rosea* extract on BE were investigated in the R+S group, that is in the animal group that exhibited BE. Indeed, the results of Experiment 4 clearly show that salidroside (administered at the amount present in 20 mg/kg of the extract) was able to significantly reduce the binge-type behavior in R+S rats for the whole period of time in which food restrictions. This finding implies that BE occurs only if repeated food restrictions have altered the regulation of brain mechanisms. These alterations induced by repeated food restrictions are essentially unknown at present; however, results of our group have provided some evidence of their occurrence. In this regard, it was recently observed that the 3 cycles of food restrictions adopted in this model result in sensitization in female rats to the hyperphagic effect of the orexigenic peptides nocipeptin/orphanin FQ and neuropeptide Y [50].

![Fig. 4.](image-url) In Panel A, effect of intragastric administration of salidroside, 624 μg/rat, or vehicle on HPF intake on the test day in R+S and NR+NS rats. In Panel B, the effect of intragastric administration of rosavin, 600 μg/rat, or vehicle on HPF intake on the test day in R+S and NR+NS rats. Data are means±S.E.M. Statistical difference: *p<0.05, vs NR+NS vehicle and **p<0.05, vs R+S vehicle.

the expression molecular chaperones of glucocorticoid receptors. In particular Hsp70 is up-regulated by *R. rosea* extracts and is responsible for inhibition of NO synthase II gene and interaction with glucorticoid receptors [34,35]. However, in regard to the short term effect observed in the present study after single administration, it is difficult to think that the observed effects might be due to interference with the gene expression of molecular chaperones, and their subsequent influence on intracellular glucocorticoid receptor activity. It looks more reasonable to hypothesize that a direct effect on the HPA axis, leading to a reduction of serum corticosterone levels may have had an important role for the effect of *R. rosea* on BE. Its effect on serum corticosterone levels may be interesting in regard to BE for two reasons: on the one hand, corticosterone has been reported to influence feeding, and in particular it has been suggested that it may be important for the expression of the hyperphagic effect of endogenous orexigenic compounds [43–45]. On the other hand, corticosterone has been shown to have motivational properties and to influence drug seeking behavior in rats [46–49], suggesting that it may have a role in the control of compulsive behavior, like that exhibited in the episodes of BE.

However, it should also be considered that in our model exposure to stress is able to evoke BE only in animals with a history of repeated stress. This hypothesis implies that BE occurs only if repeated food restrictions have altered the regulation of brain mechanisms. These alterations induced by repeated food restrictions are essentially unknown at present; however, results of our group have provided some evidence of their occurrence. In this regard, it was recently observed that the 3 cycles of food restrictions adopted in this model result in sensitization in female rats to the hyperphagic effect of the orexigenic peptides nocipeptin/orphanin FQ and neuropeptide Y [50].

![Fig. 5.](image-url) Dose–response relationship for the effect of intragastric administration of salidroside on HPF intake on the test day in R+S rats. Data are means±S.E.M. Statistical difference: *p<0.05 vs NR+NS vehicle; **p<0.05 and ***p<0.01 vs R+S vehicle.
binge-type behavior was observed. Pharmacokinetic studies have shown that salidroside is well absorbed following oral administration with a bioavailability of 32.1% in rats [56]. In dogs the half-life of salidroside has been reported to be of about 2 h [57], while two studies have shown that salidroside exhibits a half-life in rats of about 1 h [56,58]. Such a value of salidroside half-life is in keeping with its ability to control the binge episode during the whole 2-h period test. On the other hand, the effect of rosavin (again at the same dose present in 20 mg/kg of the extract) induced a lower, not statistically significant reduction of BE. These findings indicate that salidroside may represent the main active principle of R. rosea in regard to its effect on BE.

In conclusion the results of the present show for the first time that R. rosea dry extract, as well as its active principle salidroside inhibit binge-type eating in female rats, without affecting food intake in conditions in which BE was not expressed. In this regard, the effect of R. rosea is similar to that evoked by topiramate in the experimental model adopted in the present study [24]. The observed effects, together with evidence that R. rosea is not associated with overt adverse effects, suggest that its extract, or salidroside may be interesting agents for treatment of bingeing-related eating disorders.

References


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