



Genetic predisposition to obesity affects behavioural traits including food reward and anxiety-like behaviour in rats

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HIGHLIGHTS

- Rat strains that differ in their genetic predisposition to develop obesity also differ in behavioural tests linked to anxiety, exploration, and reward.
- The lean Obese Resistant rats typically displayed the most marked difference from the other strains (Sprague-Dawley, Obese Prone, and Zucker rats).
- Differences in weight within strains did not explain differences in behaviours, suggesting that weight status does not impact on behaviour.

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ABSTRACT

Here we sought to define behavioural traits linked to anxiety, reward, and exploration in different strains of rats commonly used in obesity research. We hypothesized that genetic variance may contribute not only to their metabolic phenotype (that is well documented) but also to the expression of these behavioural traits. Rat strains that differ in their susceptibility to develop an obese phenotype (Sprague-Dawley, Obese Prone, Obese Resistant, and Zucker rats) were exposed to a number of behavioural tests starting at the age of 8 weeks. We found a similar phenotype in the obesity susceptible models, Obese Prone and Zucker rats, with a lower locomotor activity, exploratory activity, and higher level of anxiety-like behaviour in comparison to the leaner Obese Resistant strain. We did not find evidence that rat strains with a genetic predisposition to obesity differed in their ability to experience reward from chocolate (in a condition place preference task). However, Zucker rats show higher motivated behaviour for sucrose compared to Obese Resistant rats when the effort required to obtain palatable food is relatively low.

Together our data demonstrate that rat strains that differ in their genetic predisposition to develop obesity also differ in their performance in behavioural tests linked to anxiety, exploration, and reward and that these differences are independent of body weight. We conclude that genetic variations which determine body weight and the aforementioned behaviours co-exist but that future studies are required to identify whether (and which) common genes are involved.

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1. Introduction

Obesity has increased markedly during the past three decades and involves a complex interplay of a number of behavioural, genetic, and environmental factors [1,2]. Over-eating disorders that

cause over-weight and obesity are increasingly viewed as brain disorders in which reward-driven urges for palatable rewarding foods “hijack” decision-making circuits [3–5]. Differences in cognitive function and in the way the reward system responds to food have been associated with variations in body mass index [5]. Consistent with this, genetic studies also point towards a role for the central nervous system in explaining obesity susceptibility [6].

Surprisingly, only few studies have explored behaviours linked to reward, anxiety or cognitive/memory function in strains of rats that differ in their genetic predisposition to develop obesity and

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that are commonly used in obesity research [7]. Indeed, it is unclear whether their obesity-predisposing genotype impacts on the development of these behaviours, as any differences detected could also be influenced by their diverging body weights. In the present study, therefore, we sought to characterize a number of such behaviours in (1) normal Sprague-Dawley rats and also in different rat strains commonly used in obesity research, namely (2) Zucker rats that carry a mutated form of the extracellular domain of the leptin receptor rendering them hyperphagic and with reduced energy expenditure [8–10] and (3) Obese Prone (OP) and Obese Resistant (OR) rats that diverge in body weight when placed on a high fat diet due to a polygenically inherited form of obesity [11]. We hypothesized that baseline genetic differences rather than differences in body weight *per se* may differentially affect behaviours linked to reward, anxiety, and cognitive function in these rat strains.

2. Material and methods

2.1. Animals

Adult male rats (age 8–12 weeks) were used for the behavioural tests: Sprague-Dawley rats (Charles River, Sulzfeld, Germany), Obese Resistant rats (CrI:OP(CD)), Obese Prone rats (CrI:OP(CD)), and Zucker rats (CrI:ZUC-*Lep^{fa}*) (Charles River, Wilmington, MA, USA). They were housed in a 12-h light/dark cycle (lights on at 6 am) with regular chow (Teklad diet 2016, Harlan Laboratories, Cambridge, UK) and water available *ad libitum* in their home cages. All animal procedures were carried out with ethical permission and in accordance with the University of Gothenburg Institutional Animal Care and Use Committee guidelines.

2.2. Experimental procedure

Behavioural testing commenced when rats of the different strains were 8 weeks old. Each test is described in full below. Two cohorts of rats, comprising all strains ($N = 12$ per strain), were compared in each cohort (Fig. 1). Cohort 1 was first tested in the elevated plus maze before commencing training for the lever pressing for sucrose paradigm, that began 4 days later. Cohort 2 was first exposed to the Open Field test and then, 2 days later, training for the conditioned place preference experiments began. Finally, in cohort 2, we performed the novel object recognition test, according to the schedule in Fig. 1. All experiments started in the morning and continued during the entire day, using a balanced design between morning and afternoon for the different experimental groups. The baseline average body weight of the different strains (in each case stated for the first followed by the second cohort) were: Sprague Dawley (SD): 309 ± 3.5 g and 332 ± 4.7 g; Obese Resistant (OR): 249 ± 3.1 g and 208 ± 2.6 g; Obese Prone (OP): 291 ± 8.1 g and 218 ± 5.2 g; Zucker rats (*fa/fa*): 334 ± 6.6 g and 265 ± 5.8 g. The body weight on the day of each behavioural experiment was also recorded.

2.3. Elevated Plus Maze (EPM)

The EPM apparatus (Med Associates Inc., St Albans, Vermont, USA) consisted of two open arms (50×10 cm²) made of black PVC (polyvinyl chloride), crossed by two closed arms (50×10 cm²) with protective walls (40 cm high), and a central platform (10×10 cm) placed elevated 70 cm above the ground. Under dim light (around 100 lx over the open arms and 60 lx over the closed arms) the rat was placed in the central platform facing to one open arm and the session lasted 5 min whereas the rat was allowed to freely move in the whole apparatus. The EPM apparatus was cleaned between each trial with 5% ethyl alcohol. The rat behaviour was recorded

by an automated system and the following parameters were determined: the number of entries into the open and closed arms (an entry was counted when the four paws were placed on the respective arm), time spent in the open and closed arms, and the number of explorations (when the upper body crossed the boundary of the open or closed arm).

2.4. Open field

This test was performed to study locomotor activity, exploration, and anxiety-like behaviour (Bailey and Crawley, 2009). In addition, the selective D_{2,3}-receptor agonist quinpirole was injected to study whether different rat strains show an altered dopamine-linked locomotor activity. After 15 min of habituation in the Open Field arena (90×90 cm) with protective Plexiglas walls (30 cm; Med Associates Inc., St Albans, Vermont, USA) corresponding to 24 h before the start of the Open Field test, each animal received an i.p. injection of vehicle (0.9% saline) or quinpirole (0.5 mg/kg) in a crossover design with at least 78 h in between: they were exposed to the Open Field for 1 h and the locomotor activity was recorded by an automated system using infrared beams in X-, Y- and Z-plane. The Open Field arena was washed with 5% ethyl alcohol between each session. The following activity parameters were measured: distance travelled, ambulatory counts, ambulatory time, vertical counts, and vertical time. In addition, the activities in the peripheral and central part (45×45) of the arena were analyzed to study anxiety-like behaviour. In addition to the behavioural changes observed after dopaminergic activation with quinpirole, the Open Field results of vehicle-injected rats were used to evaluate the strain characteristics.

2.5. Conditioned place preference (CPP)

This test was undertaken to study reward behaviour for palatable food, as described previously [12]. Briefly, a CPP apparatus (Med Associates, MED-CPP2-RS, ST Albans, VT, USA) comprising of two connected chambers ($30 \times 21 \times 21$ cm) differing in visual (white and black) and tactile (hard plastic with tactile qualities and smooth transparent plastic) cues were used, illuminated by dim light (40–45 lx) and behaviour was recorded automatically.

The CPP procedure consists of three phases: 1st phase habituation/pre-test, 2nd phase conditioning, and the 3rd phase CPP-test. During habituation the door was open between the two chambers allowing the rats to explore freely both compartments for 15 min. The second day of habituation was used as a pre-test (initial preference), in which the time spent in each compartment was recorded. The following conditioning session consisted of 20 sessions/animal (20 min each) and was conducted in 10 consecutive days in a crossover design. During the conditioning session, the least preferred compartment was paired with a rewarding/palatable food (chocolate pellets; Ms, Marabou, Kraft Foods, Upplands Väsby, Sweden) and the preferred chamber with less-rewarding food (normal chow diet). One day following the last conditioning session, the CPP test was performed during which the animals had access to both chambers without food and the time spent in each compartment was measured during 15 min. If the rat previously experienced reward from the palatable food, it will spend more time in the palatable food-paired chamber, even when the food is no longer available. All procedures were conducted in satiated animals and between each session the chambers were cleaned with 5% ethyl alcohol.

2.6. Novel object exploration

Exploratory behaviour and novel object exploration were assessed, as described previously [13]. Briefly, the apparatus com-

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