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Research report

Phenotypic profile of SWR/J and A/J mice compared to control strains: Possible mechanisms underlying resistance to obesity on a high-fat diet

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Abstract

To understand mechanisms underlying a resistance to obesity, two obesity-resistant inbred mouse strains, SWR/J and A/J, were compared to 3 inbred "control" strains, C3H/HeJ, BALB/cByJ and C57L/J. These 5 strains, studied at 5 weeks of age when similar in body weight, were maintained for 3 weeks on a 3-diet feeding paradigm, with separate jars of carbohydrate, protein and fat, or for 1 week on a single high-fat or low-fat diet. The control strains each chose a balanced diet, with 50% carbohydrate and 15–25% fat, and they had a similar, normal range of scores for measures of body weight, adiposity, endocrine parameters and metabolic enzyme activity. Compared to these control strains, the obesity-resistant SWR/J and A/J strains consumed more total calories and selected a diet with significantly more fat (35–45%) and less carbohydrate (35%). Despite overeating, they weighed less and had significantly reduced adiposity. They also had lower levels of insulin and exhibited increased capacity of skeletal muscle to metabolize fat, as indicated by measures β-hydroxyacyl-CoA dehydrogenase activity or its ratio to citrate synthase. Measurements of hypothalamic peptides via radioimmunoassay or real-time quantitative PCR revealed markedly enhanced galanin (GAL) in the paraventricular nucleus and reduced neuropeptide Y (NPY) expression in the arcuate nucleus of obesity-resistant mice. These patterns in SWR/J and A/J strains, seen on a low-fat as well as high-fat diet, may reflect mechanisms involving excess GAL and reduced NPY that contribute early, respectively, to the over-consumption of a high-fat diet and a resistance to the obesity-promoting effects of this diet.

Theme: Neural basis of behavior
Topic: Ingestive behaviors

Keywords: Dietary fat; Fat oxidation; Insulin; Obesity-resistant

1. Introduction

Most studies of mechanisms underlying eating and body weight regulation focus attention on subjects that are already obese or that are prone to obesity. Of equal importance, however, is to understand mechanisms that mediate a resistance to weight gain and body fat accrual. There is relatively little work in this area, as obesity-resistant animals are generally compared to obesity-prone subjects with higher body weight, and mechanisms underlying their resistance vs. propensity may not fall along a continuum. Thus, without a set of control animals with responses that lie within an intermediate or "normal" range, it is difficult to determine whether the differences observed between the subgroups reflect processes that produce a resistance to obesity rather than the inverse, i.e., disturbances that promote a propensity toward obesity. These control animals should have the added advantage of being closer in body weight to the obesity-resistant animals. The importance of studying the true nature of resistance has led us to turn to

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inbred mouse strains, which have been characterized and found to be differentially prone to obesity [34,39,43,46,47,49,50]. These studies have identified several strains, e.g., AKR/J, DBA/2J, and C57BL/6J, which are susceptible to the obesity-promoting effects of high-fat/high-calorie diets, and another set of strains, most notably the SWR/J and A/J, which are resistant to obesity and relatively unresponsive to these diets. Of particular interest in these investigations is a third group of inbred mice, which have no distinguishable characteristics and fall somewhere in between the prone and resistant strains. The present study used this third set of mice as an intermediate, control baseline against which the obesity-resistant mice may be compared. These control mice were equal in body weight or only slightly heavier than the obesity-resistant strains, thereby minimizing or eliminating any possible confounding effect that increased body weight or adiposity itself may have on the measures examined.

Clearly, the inbred mice constitute an important tool for investigating mechanisms that mediate a differential propensity toward obesity on a fat-rich diet [2,11,27,47]. Studies comparing a resistant to a prone strain show the obesity-resistant SWR/J mice to increase body fat only on a diet with the highest fat (45%) and lowest protein (10–20%) content, while the obesity-prone AKR/J mice accumulate greater adiposity on all dietary conditions [49]. Moreover, when given a choice of macronutrient diets, the SWR/J consuming equal amounts of fat and carbohydrate show a lower preference for fat (35–40%) compared to the AKR/J mice (>50%) [32–34] and have lower plasma glucose levels and insulin-stimulated glucose transport on a high-fat diet [9,49]. The A/J mice, generally compared to the obesity-prone C57BL/6J mice, are also relatively resistant to the obesity-promoting effects of a fat-rich diet [39,40,46]. On this diet, they have lower levels of insulin and glucose [27,40,46] and elevated uncoupling protein 1 (UCP1) and UCP2 in adipose tissue [38,46]. They also show greater sensitivity to leptin [29] and ß-adrenergic-induced thermogenesis [8] and a metabolic profile suggesting resistance to diabetes on a high-fat diet [17,30]. Whereas these results show significant differences between the strains and very likely reflect mechanisms mediating a differential propensity toward obesity, it is not clear whether such mechanisms are specific to the resistance phenotype. Furthermore, with the marked differences in body weight between the prone and resistant strains in these reports, the differences observed in the various measures may, in part, be a consequence of the differential level of adiposity in these animals.

Thus, to minimize the impact of this body weight difference while focusing attention on mechanisms underlying a resistance to obesity, we made specific efforts in the present investigation to establish a set of control mice, which may be used as a baseline for direct comparisons with a set of obesity-resistant mice. To our knowledge, there are no studies of this nature. The strains selected for this control baseline were amongst the set of mice found to have specific behavioral patterns falling in between the resistant and prone animals. These strains, C3H/HeJ, BALB/cByJ, and C57L/J, show moderate weight gain and total intake on a high-fat/high-calorie diet [34,48] and, as demonstrated so far for BALB/cByJ and C57L/J, spontaneously select a balanced diet with a stronger preference for carbohydrate over fat when given macronutrient diets [34,50]. These inbred strains were examined to determine whether they provide stable behavioral, endocrine, metabolic measures that are suitable as a control baseline. The two obesity-resistant strains, SWR/J and A/J, were then characterized to determine whether they exhibit phenotypes that are different from the control strains and possibly from each other. With few reports comparing inbred mouse strains with respect to their hypothalamic peptides, measurements of galanin (GAL) and neuropeptide Y (NPY) were also taken. These mice were tested starting at 5 weeks while still of equal body weight to determine whether differences can be detected at a young age and thus presumed to be causally related to the differential weight gain. They were also examined under different dietary conditions, involving pure macronutrient diets, a single high-fat diet and a low-fat, chow diet.

2. Materials and methods

2.1. Animals

Five male, inbred mice strains (C3H/HeJ, C57L/J, BALB/cByJ, A/J, SWR/J) were purchased at 4 weeks of age from The Jackson Laboratory (Bar Harbor ME). The mice were individually housed in Experiments 1–3 and group housed in Experiment 4 and Experiment 5 (n = 6/cage) in Plexiglas cages containing bed o-cobs in a fully accredited AAALAC facility (22 °C, with lights off at 3:30 p.m. for 12 h), according to institutionally approved protocols as specified in the NIH *Guide to the Use and Care of Animals*. Both food and water were available ad libitum. Mice were maintained on rodent chow for 1 week before the start of the experiment. In Experiments 1–3, they were switched to pure macronutrient diets for 3 weeks and then sacrificed. In Experiment 4, they were given a single, high-fat diet for 1 week, while in Experiment 5 they were maintained on a low-fat chow diet for 1 week and then sacrificed.

2.2. Diets

Two different feeding paradigms were used, with a single high-fat diet or 3 macronutrient diets available ad libitum and diet composition calculated as percentage of total Kcal. In the 3-diet choice paradigm, the protein diet (3.7 Kcal/g) consisted of 93% casein (Bioserv) mixed with 4% minerals (USP XIV Salt Mixture Briggs, I.C.N. Pharmaceuticals), 2.97% vitamins (Vitamin Diet Fortification Mixture, I.C.N. Pharmaceuticals), and 0.03% cysteine (L-cysteine hydro-