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Differences in the Body-Mass and Fat Composition of NK1R–/– ('knockout') Mice and their Wild types is Consistent with an Increased Vulnerability to Comorbid Obesity in ADHD Patients

In previous studies, we have found that mice lacking functional neurokinin–1 receptors (NK1R–/–) are *hyperactive*, compared with their wild types (e.g., 1). They also have a higher incidence of *premature responses* (an index of motor impulsivity) and *omission errors* (an index of inattentiveness) when tested in the 5–Choice Serial Reaction Time Task (e.g., 2). These abnormal behaviours are arguably analogous to those seen in patients with Attention Deficit Hyperactivity Disorder (ADHD). This proposal is supported by evidence that polymorphism(s) of the human *TACR1* gene, which is the human equivalent of the rodent *nkr1* gene, increase vulnerability to ADHD (3). Although small body¬-size is possibly a risk factor for ADHD, co-morbid obesity is common in these patients (e.g., 4). Prompted by this evidence, we compared the body-size, body-mass and %fat of NK1R–/– and their wild type mice.

All measurements were carried out on NK1R-/- and wild type mice, of both sexes (background strain: C57BL/6Jx129/Sv with MF1 backcross) that had been fed either a normal or high–fat ('Western') diet. Two cohorts of mice (N=8-10 for each genotype and sex per cohort) were weaned onto either normal laboratory chow (2018 global Rodent Diet, Harlan) or high–fat chow (fat comprised 45% of total calorific intake; Research Diets, NJ, USA). The mice were killed at either 6 (normal diet) or 7 weeks (high–fat) of age and their weight and body-length recorded. The carcasses were stored at –20°C before chemical analysis of milled, freeze–dried samples using a modified Soxhlet extraction protocol. The data were analysed by 2-way ANOVA (with repeated measures, when appropriate), and *posthoc* Fisher's LSD (least significant difference) tests.

NK1R-/- mice were shorter (*c.* 9%) than wild types, regardless of sex or diet ($F(1,36)=53.9$; $P<0.001$). Male NK1R-/- mice fed the normal diet weighed less than their wild types (*c.*9%; $P=0.03$; main effect of genotype: $F(1,36)=5.75$; $P=0.02$). However, when fed the high-fat diet for 28 days, the weight of male NK1R–/– and wild type mice did not differ. Moreover, female NK1R-/- mice on the high-fat diet weighed more (*c.*11%; $P=0.002$) than their wild types (geno*sex: $F(1,33)=5.59$, $P=0.02$). Both male and female NK1R–/- mice, on either diet, had a higher body density (g/cm^2: 'mBMI') than wild types(10-15%: normal diet: $P<0.001$; high–fat: $P<0.001$). On the high-fat diet, %fat of male, but not female, NK1R–/– mice was higher than that of wild types (40%: $P<0.001$).

These data suggest that, when compared with wild types, mice lacking functional NK1R have a smaller body size and that male NK1R-/- mice have a greater proportion of body fat. The findings further suggest the possibility that patients with polymorphism(s) of *TACR1* comprise a subgroup of ADHD patients who have a small body size and increased vulnerability to co-morbid obesity. If so, drugs that augment *TACR1* function, or that of their downstream targets, might help to resolve both ADHD and obesity in these patients

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