Table 1. Summary of weight measurements

STRAIN	total weight TW (g)	adiposity index*	kidney/100 g TW	liver/100 g TW
BN/Cub (N = 6)	261.5 ± 5.2	0.85 ± 0.03	0.56 ± 0.01	2.55 ± 0.02
BN-*Lx* (N = 9)	302.4 ± 4.8	0.74 ± 0.03	0.53 ± 0.02	2.46 ± 0.05
BN.SHR4 (N = 6)	268.0 ± 17.8	0.96 ± 0.06	0.58 ± 0.02	3.39 ± 0.13
BN-*Lx* 1K (N = 7)	254.8 ± 2.91	0.72 ± 0.01	0.56 ± 0.01	2.73 ± 0.05
P (ANOVA)	**P < 0.05**	**P < 0.001**	**ns**	**P < 0.0001**

Values are given as mean ± SEM. *The adiposity index is calculated as epididymal fat pad weight/100 g TW. P (ANOVA) represents the analysis of variance, values show the significance of differences among strains.

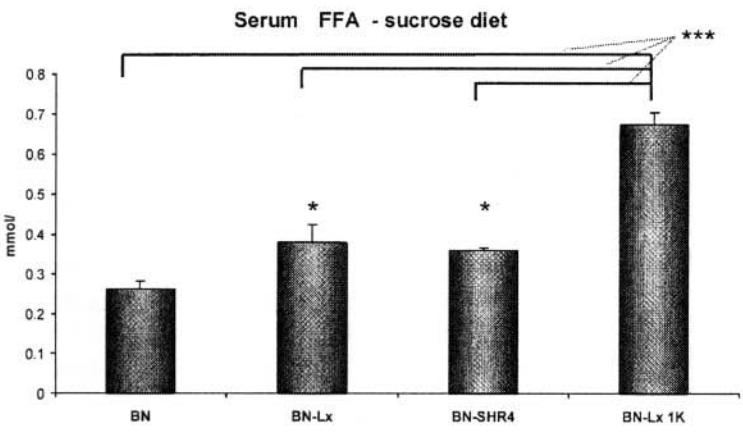

Fig. 5. Serum FFA concentrations (mmol/l) in not fasted animals after high-sucrose diet. Values are given as mean ± SEM. Significant differences are shown as follows: *...P < 0.05, **...P < 0.01, ***...P < 0.001. Signs over the columns refer to comparisons with the BN/Cub strain.

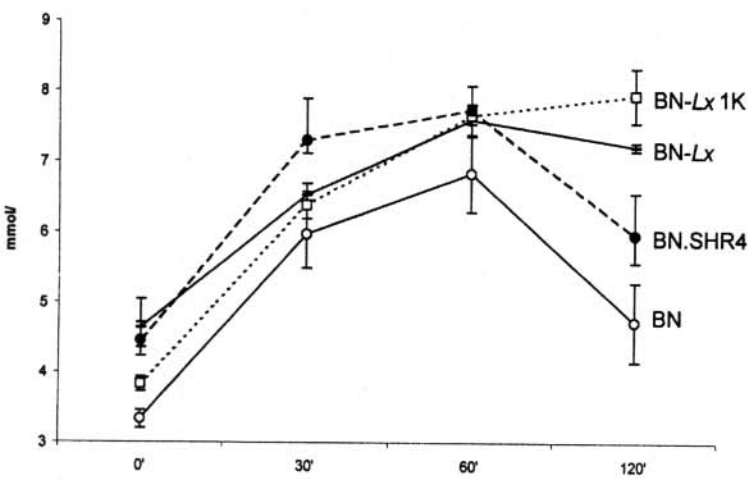

Fig. 6. Oral glucose tolerance test after high-sucrose diet. Values are shown as mean ± SEM. BN solid line (○), BN.SHR4 dashed line (●), BN-*Lx* solid line (-), BN-*Lx* 1K dotted line (□). For AUCs and ANOVA testing, see Table 2.

genic strain and highest in **BN.SHR4** congenic strain (0.716 ± 0.011 and 0.955 ± 0.059, respectively). The weight measurements are summarized in Table 1.

Discussion

The genetic contribution to the development of insulin resistance, obesity and dyslipidemia is well established, but the extensive search for particular genes responsible for the prevailing forms of these diseases has not yielded persuasive results. Genetically defined animal models allow us to partially overcome the complexity of human disease and could possibly provide deeper insight into the pathophysiological mechanisms involved. The rat is „an important model organism for systems biology research" and since „the Rat Genome Project has been rapidly gaining momentum during the past five years", „the rat genome can be annotated with biological functions that can relate to complex disease" (Jacob and Kwitek, 2002). At the present time, there are several feasible rodent models of IRS features available, mentioned above. Inbred model strains represent specific genetic combinations leading, in interaction with environment and other factors, to the manifestation of the particular disease phenotype. The alleles responsible for this phenotype may be unique for individual strains, but some may „overlap" and be present in several strains. In the case of complex traits with the oligo- or polygenic type

of inheritance, analysis of a particular animal model could thus elucidate different facets of the genetic determination of a studied trait.

In this study we investigated the influence of transferring of several chromosomal segments, previously reported to contain QTL affecting carbohydrate and/or lipid metabolism, onto the genetic background of the normotensive, normotriglyceridemic **BN/Cub** strain. As expected, we found that such transfer leads to a significant rise in serum triglycerides and non-esterified fatty acids with a tendency for aggravation of dyslipidemia when more QTLs were present. The same was true for impairment of glucose tolerance, assessed by OGTT.

One of the studied candidate genes for dyslipidemia and insulin resistance is *Cd36/FAT*, encoding fatty acid translocase. The CD36 was during the last 25 years of study established as a multiligand receptor involved in a variety of physiological processes, including cellular adhesion, fatty acid and lipid transport, utilization, and storage, antigen presentation, and clearance of apoptotic cells and shed photoreceptors (Febbraio, 2001). The spontaneously hypertensive rat strain was shown to carry a mutant allele of the *Cd36/FAT* gene, which is suggested to be responsible for the metabolic disturbances found in this strain (Aitman et al., 1999; Pravenec et al., 2001). In our study, two congenic strains (**BN.SHR4** and **BN-*Lx* 1K**) carried the *Cd36/FAT* gene of **SHR** origin within the differential segment on the **BN/Cub** genetic background. Our results further support the importance of this chromosomal region in dyslipidemia and insulin resistance and the newly established **BN.SHR4** congenic strain represents a useful tool for its analysis.

The region of rat chromosome 8 of **PD/Cub** origin present on the **BN/Cub** genetic background of two congenic strains in this study (**BN-*Lx*** and **BN-*Lx* 1K**) carries, among others, the *ApoA-I/ApoC-III/ApoA-IV* gene cluster. This region of the rat genome (Gauguier et al., 1996; Okuno et al., 1999) and its syntenic counterparts in mouse (MMU9) and human (11q22-23) were previously related to metabolic disorders (Norman et al., 1997, 1998; Fisher et al., 1999).

The impact of the *ApoA-I/ApoC-III/ApoA-IV* gene cluster on lipid metabolism and atherogenesis has been documented in human studies, as well as in transgenic mice overexpressing either *ApoC-III* (Ito et al., 1990; Shachter, 2001), *ApoA-I* (Walsh et al., 1989), *ApoA-IV* (Duverger et al., 1996), or the whole *ApoA-I/ApoC-III/ApoA-IV* gene cluster (Vergnes et al., 2000). Furthermore, another gene coding for apolipoprotein A-V has just recently been localized in the immediate vicinity of this cluster and shown to be an important determinant of plasma triglyceride levels in human and rat (Pennacchio et al., 2001; van der Vliet et al., 2001). We observed deterioration of the metabolic profile of congenic strains carrying the differential segment from a recently established model of insulin resistance and dyslipidemia, the **PD/Cub** strain. This proves the presence of the allele(s) influencing this complex trait within this region of **PD/Cub** chromosome 8 and following research will focus on determination of the responsible gene, *ApoA-I/ApoC-III/ApoA-IV/ApoA-V* gene cluster being the preliminary candidate.

With respect to the described metabolic influence of the two above mentioned chromosomal regions it is of interest that the **SHR-*Lx*** congenic strain, in which the differential segment of **PD/Cub (BN-*Lx*)** chromosome 8 was introgressed onto the **SHR** genetic background, after one week of high-sucrose diet feeding shows even higher levels of FFA than its progenitor strains, suggesting an additive effect of these two loci (Šedová et al., 2000b).

An interesting observation was made concerning the adiposity index, where the triple congenic strain **BN-*Lx* 1K** showed the significantly lowest adiposity index, together with the highest concentrations of TG, FFA and the most profound insulin resistance. The adiposity index is considered to be a reliable marker of visceral obesity, which is often associated with other risk factors of cardiovascular disease. The **SHR.1N** congenic strain, where a segment of **BN-*Lx*** chromosome 20 was transferred onto the genetic background of **SHR** (and a QTL for hypertension was located within this relatively large (30 cM) segment by Pravenec et al. (1989)), was reported to be more prone to obesity when compared to the **SHR** progenitor (Pausová et al., personal communication). Taken together, it is likely that within the differential segment on RNO20 lies a candidate gene involved in diet-induced obesity, *Tnf-alpha* (Pausová et al., personal communication) being the preliminary candidate.

Carbohydrate-induced hypertriacylglycerolemia is a phenomenon described since the 1950s (recently reviewed in Parks and Hellerstein, 2000, Hellerstein, 2002). However, the understanding of its underlying mechanisms is still somewhat clumsy. Precisely defined animal models can help elucidate at least several aspects of this condition. In our study, we observed distinct elevations of triglyceride levels in response to high-sucrose diet intervention. It is therefore possible to assume that genes present in the differential segments of **BN/Cub**-congenic strains are likely to be involved in this complex process. Furthermore, we can speculate that apart from gene-environment interactions (i.e. the interaction of genes in differential segments predisposing for susceptibility to environmental influence - sucrose diet), there exists an interplay of gene-gene interactions (combination of differential segments on the **BN/Cub** genetic background led to substantially increased reaction not always explainable by a simple additive effect).