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Rat Models of Metabolic Syndrome

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Abstract

Metabolic syndrome is a complex disorder that is comprised of several other complex disorders, including obesity, hypertension, dyslipidemia, and diabetes. There are several rat models that encompass component features of MetS. Some models are inbred strains selected for one or more traits underlying MetS; others are population models with genetic risk for MetS traits, are induced by environmental stressors such as diet, are spontaneous monogenic mutant models, or are congenic strains derived from a combination of these models. Together they can be studied to identify the genetic and physiological underpinnings of MetS to identify candidate genes or mechanisms for study in human MetS subjects.

1. Introduction

The Metabolic Syndrome, sometimes referred to as Syndrome X or MetS, is a coincident occurrence of disorders that substantially increase the risk for mortality from heart disease, stroke, and renal failure. Syndrome X was described by Reaven in 1988 as the cooccurrence of insulin resistance, hyperglycemia, hyperinsulinemia, hyperlipidemia and hypertension [1]. While the specific clinical criteria have been debated over the past three decades, the internationally recognized clinical diagnosis for Metabolic Syndrome is three or more of the following: elevated waist circumference (a measure of abdominal obesity); elevated triglycerides; reduced high-density lipoprotein (HDL) cholesterol; elevated blood pressure; elevated fasting glucose [2]. Globally, the prevalence of MetS is estimated to be 25% [3] and its prevalence in children and young adults is estimated at 6.5% [4]. While these numbers vary by population and by criteria used to define MetS, the dramatic increase over the past two to three decades is a major health concern.

While MetS is a syndrome in name, it is actually a complex disorder that is comprised of several other complex disorders, including obesity, hypertension, and diabetes. MetS is caused by both heritable and environmental influences [5-7]. Each defining feature of MetS also has a genetic component, with strong influences by environmental stimuli [6,5,8]. To effectively treat hypertension in MetS, it is important to determine what genes and mechanisms underlie MetS and its individual components, a goal that is substantially

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benefitted by physiological and genetic studies in animal models of MetS and/or its defining traits.

There are several rat models that encompass component features of MetS. Some models are inbred strains selected for one or more traits underlying MetS; others are population models with genetic risk for MetS traits, are induced by environmental stressors such as diet, are spontaneous monogenic mutant models, or are congenic strains derived from a combination of these models. Together they can be studied to identify the genetic and physiological underpinnings of MetS to identify candidate genes or mechanisms for study in human MetS subjects.

Some rat strains have several MetS traits, allowing for identification of putative pleiotropic genes while some have only a small subset, avoiding the confounding effects of other MetS traits. A comprehensive list of rat strains was annotated as obesity/metabolic syndrome models in the Rat Genome Database Obesity Portal [9]. Table 1 lists examples of different strains with two or more MetS traits, along with their defining features of MetS. Because waist circumference is not readily translatable to rats, obesity was included as a defining feature. Because of species differences in lipid profiles between human and rats [10-12], increased total cholesterol was included with low HDL as a defining feature of MetS for this review. Below are some examples of the different rat models of MetS.

2. Inbred selection models of MetS

Selective breeding followed by inbreeding has been used to generate numerous polygenic models of human behaviors or conditions in rats ranging from learning and alcohol preference to hypertension and diabetes [13-16]. Selective breeding involves identifying and breeding animals with a specific trait over several generations, thereby ‘fixing’ the genetic factors contributing to the trait. Subsequent inbreeding while maintaining the trait results in a genetically predisposed inbred strain that can be used in physiological and genetic studies. There are several inbred selection rat models that have all or a subset of characteristic features of MetS.

The **Lyon Hypertensive** (LH/Mav; RGDID:10021) rat model was selectively bred for spontaneous hypertension from a small founder population of six SD rats [17]. Selection for normotensive (LN/Mav; RGDID:10022) and hypotensive (LL/Mav; RGDID:1581645) rats were done in parallel from the same founders. After as few as three generations of selection, LH rats were indeed spontaneously hypertensive, LN rats were normotensive, and LL were hypotensive. However, upon further inbreeding, the LL rats lost the hypotensive phenotype but remained normotensive, providing a second control strain for the LH strain [18,19]. LH rats are both spontaneously hypertensive and salt sensitive [20]. Further study determined that, in addition to hypertension, LH rats have increased body weight, serum lipids including triglycerides and cholesterol, and altered insulin/glucose ratios [21,22] compared to the LN control strain. While initial studies indicate the LH rat is not diabetic or insulin resistant [23], we demonstrate male LH/MRrrcAek (RGDID:10755352) rats have altered glucose tolerance (Fig 1A) and are hyperinsulinemic (Fig 1B) compared to the control male LN (LN/MRrrcAek; RGDID:10755354) rats when fed a low fat diet (D12450H, Research Diets,

Inc.). Overall, the LH strain is a comprehensive MetS model for both physiological and genetic studies. Comprehensive genetic studies in the LH rat determined that MetS is polygenic, with both independent and pleiotropic genetic effects on MetS traits, and combined fine-mapping and systems genetic studies have identified multiple loci and candidate genes [24,22,25-28].

The WOKW (**Wistar Ottawa Karlsburg W** (RT1u); RGDID:67935) and OLETF (**Otsuka Long-Evans Tokushima Fatty**; RGDID:61014) rat strains are also spontaneous genetic models of MetS with obesity, hypertension, hypertriglyceridemia, abnormal plasma cholesterol levels, glucose intolerance, and hyperinsulinemia [29-34]. Through genetic mapping and fine-mapping in congenic strains, several QTL and candidate genes for MetS traits have been identified in WOKW [35-37] and OLETF rats [34,38-40,33]. Both strains have spontaneous risk for all major features of MetS, although the progression can be associated with age and sex. Interestingly, the OLETF was found to have a spontaneous mutation in the CCK1 receptor that contributes to its hyperphagia and obesity [41].

The **Spontaneously Hypertensive Rat** (SHR; RGDID:61000) is arguably the most comprehensively studied model of genetic hypertension with over 19,000 publications in PubMed (query SHR AND rat). Like the LH rat, SHR rats are also genetically predisposed to several features of MetS including hypertension and dyslipidemia [42-47] although they are not generally considered obese. The breeding history of the SHR is complex, and over 40 substrains of SHR are annotated in the Rat Genome Database. The stroke-prone SHRSP strains are well recognized SHR substrains derived from SHR progenitors with spontaneous stroke and then inbred. There are over 20 substrains of SHRSP. Gene identification using traditional positional cloning, comprehensive systems genetics, and gene targeting have been an active area of study in the SHR rat [48,45,49]. Dysregulation of several genes involved in MetS related traits have been identified in the SHR rat through genetic and genomic approaches (e.g. *CD36, Ogn, Srebpf*, *Folr1)*, and validated in transgenic and gene targeted models [50,51,49,52].

There are several additional inbred selection strains having a subset of MetS traits. For instance, the **Prague hereditary hypertriglyceridemic** (HTG; RGD ID:1302795) strain is a non-obese model with high plasma triglycerides, hypertension and insulin resistance [53-55]. This model was selectively bred for high plasma triglycerides on a high-sucrose diet, suggesting possible pleiotropic genetic effects on regulation of lipids, blood pressure, and glucose, although genetic mapping studies failed to identify a single locus involved in all phenotypes [56,53]. The **Polydactylous** rat strain (PD/Cub; RGDID:728161) has a spontaneous mutation causing polydactyly-luxate syndrome, but also shows features of MetS, including increased adiposity, insulin resistance and hypertriglyceridemia [57]. A comprehensive genetic study that included dietary and pharmacologic stressors in an intercross between PD/Cub and BN/Cub identified several loci for MetS related traits, some with independent effects and others showing epistatic interactions [58].

Two non-obese, spontaneously diabetic rat strains are the **Spontaneously Diabetic Torii** (SDT/Jcl; RGDID: 631219) and **Goto-Kakizaki** (GK/Jcl; RGDID: 13506737) strains. The SDT strain is a Type 2 diabetes model that also shows hypertriglyceridemia severe diabetic

retinopathy, nephropathy, and neuropathy [59,60]. Several loci for hyperglycemia and glucose intolerance and diabetes have been identified in SDT rats [61,62], and genetically induced islet inflammation is thought to play a role in developing diabetes [61]. Glucose intolerance and Type 2 diabetes in the GK rat have been extensively studied, and further studies revealed the GK strain also shows increased basal blood pressure compared to Wistar controls and salt sensitivity [63]. Several genetic loci have been identified that regulate not only the GK phenotypes but also its transcriptome and metabolome [64,65]. Furthermore, the specific genetic contributions evolve over the lifetime of the animal and the disease progression [66,67]. There are over 10 different substrains of GK rat annotated in the Rat Genome Database or reviewed in Portha and colleagues [66]; therefore, one must be cognizant of the substrain(s) being studied as there are substantive phenotype differences between them [66].

3. Diet Induced Models of MetS

Most of the models described above show spontaneous features of MetS. However, induced models also exist whereby MetS traits are only evident after an environmental stressor such as diet. For example, when the inbred **Cohen Rosenthal Diabetic Hypertensive** rats (CDRH; RGDID:68019) are fed a high-sucrose, copper-poor diet, they become hypertensive and diabetic but not obese [68]. This strain was derived by crossing Cohen Diabetic Rats (CDR; RGDID:1357178) with SHR rats, then selectively breeding for both high blood glucose and high blood pressure for several generations while being fed the copper-poor, high sucrose diet. This unique model has been used to study the effects of various anti-hypertensives on metabolic parameters in diabetic hypertension [69-71].

The **Dahl Salt Sensitive** rat (SS; RGDID:69369) is likely the most studied salt-induced hypertension model, with nearly 3000 publication (query Dahl AND rat). While SS rats are a well-established inbred model of salt sensitive hypertension, studies have also found SS rats display insulin resistance and dyslipidemia on normal and high salt diets ([72,73]; further reviewed in [74]). Furthermore, SS rats can develop hypertension, insulin resistance, and dyslipidemia when fed diets high in fat, fructose and/or sucrose [75-78]. Finally, dietary protein levels and even protein source influences the phenotypes of SS rats. A low-protein diet or replacing casein with wheat gluten as the dietary protein source lowered both blood pressure and body weight, potentially through modulation of the immune system [79,80].

Some outbred strains also show diet induced MetS. The two most prevalent models are **Sprague Dawley** (SD; RGDID:70508) and **Wistar** (WI; RGDID:13508588) rats fed high energy (fat and/or sugar) diets, sometimes called DIO rats [81-83]. The SD DIO rats were developed after the observation that SD rat populations show a bimodal body weight distribution when fed a high energy diet [84]. Levin and colleagues performed several generations of selective breeding in the obesity prone SD rats to develop the DIO and in the obesity resistant SD to develop the DR rats, with both lines being fed a diet high in fat and sucrose [81]. While they went through selection, there is not clear evidence that isogenic inbred strains were developed. Nevertheless, in addition to increased body weight and adiposity, most features of MetS have been observed in SD derived DIO rats including glucose intolerance, dyslipidemia and hypertension [85,81]. Another outbred strain

identified to have a bimodal weight distribution on high fat diet is the Wistar strain. Studies of diet induced obesity using this model continue to be performed in commercially available outbred Wistar rats, stratified into diet induced or diet resistant categories after exposure to the obesogenic moderately high fat diet with or without high sugar [86-88]. Again, all features defining MetS have been observed in the Wistar DIO rats (reviewed in [89]). Of note, the Wistar DIO rats show evident sex differences [86].

Outbred rats such as SD and Wistar are often studied to recapitulate the heterogeneity of human populations. However, we and others have shown that phenotypes in outbred strains vary widely by source due to differing breeding histories of the strains; therefore, care must be taken when generalizing results from strains such as SD from differing vendors as they do not represent the same population sampling [90,91].

4. Population Models of MetS

Another unique source of outbred rats was first developed by Hansen and colleagues at the National Institutes of Health (NIH), called **N/NIH heterogeneous stock** (HS) (RGDID:728185; [92]). HS rats are descendants of founders from eight inbred strains - ACI/N, BN/SsN, BUF/N, F344/N, M520/N, MR/N, WKY/N and WN/N – that represent high genetic diversity and span the phylogenetic tree of the laboratory rat [93]. Crossbreeding between these eight founder strains was performed to minimize inbreeding and thus maximizing genetic diversity in the heterogeneous stock, making them a strong population model which is also amenable to genetic studies. While no intentional phenotypic selection was performed in the development of N/NIH, they have been shown to segregate many traits [94-96]. An advantage of the HS rats is that they segregate many traits without intentional selection. They are thus a strong model for human population studies of exposures, for example to drugs and chemicals. The conditions most studied in HS rats include those related to psychiatric disorders and substance abuse, but also include symptoms of MetS. Solberg Woods and colleagues have performed extensive phenotyping and genotyping of HS rats, followed by genome wide association studies to identify loci and candidate genes for adiposity and glucose homeostasis in HS rats [97,98].

In the mid-1990s Drs. Koch and Britton selectively bred the N/NIH rats for low and high capacity exercise endurance, respectively [99]. Different from many selection models, the **Low Capacity Runners** (LCR; RGDID:2314396) and **High Capacity Runners** (HCR; RGDID:2314397) rats have been intentionally maintained as outbred stock. These rats have been extensively studied at the physiological level and studies determined the LCR rats are a robust MetS model [100,101]. Genetic studies suggest high heritability of several metabolic traits and the potential of QTL mapping in crosses between LCR and HCR [102].

5. Genetic Models of MetS

Models of human disease often arise through spontaneous or targeted mutation of a gene that is sufficient to cause a phenotype. The most prominent monogenic rat models of MetS arose through two independent spontaneous mutations in the gene encoding the leptin receptor (*Lepr*). The **Obese Zucker** rat (ZUC-Lepr^{fa}; RGDID:629464) was described in the early

1960s [103] as a spontaneously obese rat in an outbred colony that was later found to be due to a homozygous missense mutation (Gln269Pro) in *Lepr* [104], called *fatty* or *fa* that resulted in constitutive receptor activity [105]. Several other rat strains were derived from the Obese Zucker rat that included other MetS traits. The **Zucker Diabetic Fatty Rat** (ZDF-Lepr^{fa}/Drt; RGDID:12859287) originated from the original Zucker colony by selecting breeding rats that were both obese and diabetic [106]. Inbred MetS strains with the *fa* mutation include the obese diabetic **KZF** (KZ-Lepr^{fa}/Tky; RGDID:1302693) and models where the *fa* allele was bred onto hypertensive strains such as the SS (**SS.ZUC-Lepr$^{fa-/-}$/Slc**; RGDID:13432148) and SHRSP (**SHRSP.ZUC-(D5Rat4-D5Rat36)/IzmDmcr**; RGDID: 2300018) and show all defining MetS features [107,108].

The *cp* or *corpulent* allele of *Lepr* was identified in the **Koletsky** or **Obese SHR** rat strain (SHROB/KolGmiCrl-Lepr^{cp}; RGDID: 2311049) which arose as a spontaneous *Lepr* mutation in a cross between a hypertensive SHR female and a SD male [109]. These rats were obese, hypertensive and dyslipidemic but not diabetic [110]. The *cp* mutation was found to be a nonsense mutation, causing truncation at amino acid position 763 [111]. The *cp* mutation has also been bred into the **Diabetes Resistant BioBreeding** (BBDR/Rhw; RGDID: 10003) rat to develop an obese, hypertensive, dyslipidemic, diabetic model (**BBDR.LA-(D5Rat98-D5Rat233)/Rhw**; RGDID: 6893530), where the phenotype was found to be sex-dependent [112].

While the leptin receptor mutant rats were the only monogenic model of MetS for decades, transgenic rat models were developed to study MetS traits, for example transgenic expression of *Cd36* and *Srebf1* in the SHR (RGDIDs: 2302148-2302151; RGDIDs: 2300216, 2313693) [113,114] and SS rats overexpressing human *CETP* (RGDID: 2290429) [115]. Furthermore, the successful culture of rat ES lines [116,117] and other applications of targeted mutagenesis (e.g. using Zinc Finger Nucleases, TALENS, or CRISPR-Cas9) is opening up new opportunities to study pathobiological mechanisms in single gene rat MetS models [118-121], including melanocortin receptor (*Mc3r* and *Mc4r*) and ghrelin receptor (*Ghsr*) mutations in outbred Wistar rats and Angiopoietin-like protein 8 (*Angptl8*) in inbred F344 rats [122-124].

6. Notes

Herein we described numerous rat models that display key features of the human metabolic syndrome. The models range from single gene mutations, to inbred selection models with polygenic inheritance, to population models that perhaps best mimic the heterogeneity of human MetS. Each model has its own benefits and limitations. Some models have all defining traits of MetS and could be useful for identifying gene pleiotropy or common underlying pathophysiology linking seemingly independent traits. However, identifying which mechanism(s) are causal may be confounded by the presence of other traits. The population models may better represent the general human clinical condition and can map traits to smaller genomic intervals than is possible with other approaches such as F2 intercrosses. A disadvantage of these models is that once a locus is identified, identifying the causal variant(s) can be confounded by a mixed genomic background. Single gene models can facilitate thorough mechanistic understanding of the resulting phenotype. However,

single gene MetS disorders are extremely rare in humans and do not represent the highly complex genetic, epigenetic, and environmental contributions to MetS. As such, one must carefully consider which type of model answers the research question at hand. Regardless, the rat is a rich resource for polygenic models such as the metabolic syndrome.

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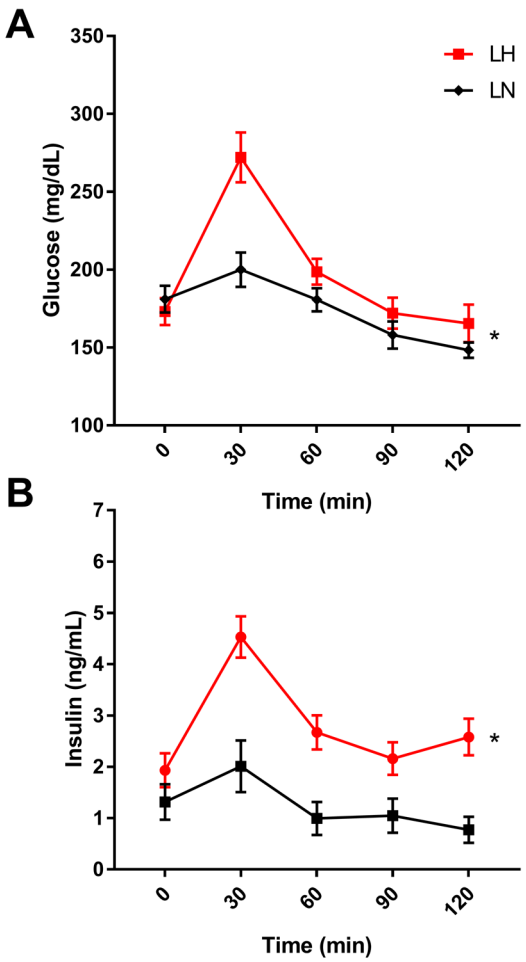

Figure 1:

Male LH/MavRrrcAek rats are glucose intolerant and hyperinsulimemic compared to LN/MavRrrcAek rats. Rats were fed a 10% fat diet (Research Diets D12450H) from wean. At 12 weeks of age Intraperitoneal Glucose Tolerance Tests (IPGTT) were performed on animals fasted 6 hours (+/− 0.5 hr) then given 2g glucose/kg body wt IP. Blood glucose and insulin levels were measured at 0, 30, 60, 90 and 120 minutes following glucose challenge. * $P < 0.05$, two-way ANOVA.

Table 1:

Selected Rat Models of Metabolic Syndrome. TC = Total cholesterol; HDL = high density lipoprotein cholesterol; LDL = low density lipoprotein cholesterol. Strain details are provided in the text.

			Traits Defining Metabolic Syndrome				
Strain	**Disease Type**	**Strain Type**	**Hypertension**	**Obesity/ ↑Adiposity**	**Hyperglycemia/ Glucose intolerance/ Insulin resistance**	**Elevated triglycerides**	**Reduced HDL/ Increased TC**
LH	Spontaneous	Inbred selection	√	√	√	√	√
WOKW	Spontaneous	Inbred selection	√	√	√	√	√
OLETF	Spontaneous	Inbred selection	√	√	√	√	√
SHR	Spontaneous	Inbred selection	√		√	√	√
HTG	Spontaneous	Inbred selection	√		√	√	
PD/Cub	Spontaneous	Inbred selection		√	√	√	
GK	Spontaneous	Inbred selection	√		√		
SDT	Spontaneous	Inbred selection			√	√	
CRDH	Diet induced	Inbred	√		√		
Wistar	Diet induced	Outbred	√	√	√	√	√
SD	Diet induced	Outbred	√	√	√	√	√
Obese Koletsky	Monogenic	Inbred	√	√	√	√	√
Obese Zucker	Monogenic	Inbred		√	√	√	√
ZDF	Monogenic	Inbred		√	√		

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