

Diet-Induced Hypertension in Rodent Models

2018 - Brief Scientific Literature Review

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Hypertension is among the most common causes of mortality in both developed and developing countries, and its prevalence has been on the rise (1). Although this disease is widely studied, the pathogenesis of hypertension in humans is not completely understood. To better understand the specific mechanisms involved, as well as to research treatments for prevention/cure of hypertension, various animal models have been developed to mimic the hypertensive response seen in humans.



As in humans, diet choice influences the hypertensive response in rodent models. In rodent models, there are 2 basic diet choices: Purified ingredient diets and grain-based (GB) diets. Purified diets have been used quite effectively for driving hypertension in various rodent models. As the name implies, purified ingredient diets are made with highly refined ingredients, each of which provides one main nutrient, allowing them to be well-defined, consistent, and easily modified. In contrast, GB diets contain unrefined grains and animal byproducts, each of which contains multiple nutrients and non-nutrients (2).

The preferred animal model is the rat due to the amount of published physiological data, relatively small size, and robust responses of some genetic strains. Numerous rat models have been developed to study hypertension including selectively-bred homozygous rat strains such as the Spontaneously Hypertensive Rat (SHR) and Dahl Salt Sensitive (Dahl SS) rat as well as outbred strains such as the Sprague Dawley (SD) rat. Because these different rat models develop hypertension differently, researchers need to consider this when deciding upon which rodent strain to use (3). In this brief review, we show how dietary factors influence the hypertensive phenotype in different rodent models of hypertension.

Diet-Induced Hypertension

Rats

Typical levels of sodium chloride in a purified ingredient diet ranges between 0.3-0.4%. Lewis Dahl fed selectively-inbred SD rats an 8% GB NaCl diet, and depending on their response, segregated them into the Dahl SS and Dahl Salt-Resistant (Dahl SR) rat models (4). Weaned Dahl SS rats fed an 8% GB NaCl diet develop elevated blood pressure (>180 mm Hg, typical levels on a GB diet is ~ 120 mm Hg) in about 4-6 weeks, though some of these animals may show such elevation within as little as 2 weeks (4-7). Typically, after 6 weeks on a high-NaCl diet, blood pressure falls, and clinical heart failure develops in these animals. When fed lower levels of NaCl (0.4-2%), hypertension develops along with vascular and renal lesions, although the time period is typically longer (8, 9). The age of the animal also seems to play a role in the development of NaCl-induced hypertension.



A high NaCl diet (8%) started at 3 or 6 months after weaning elevates blood pressure, though at a slower rate than those placed on the diet at weaning. However, none of the animals typically survive beyond 8 months on an 8% NaCl diet regardless of the age at which they start (8). Dahl also observed that the responses to excess NaCl were greater in males than in females (4). In stark contrast, the Dahl SR rat failed to exhibit elevated hypertension or vascular/renal lesions even after being placed on an 8% NaCl diet for several months (4, 9-11).

Diets containing normal levels of NaCl (0.3-0.4%) but high levels of fructose or sucrose (around 60% of calories) can also increase blood pressure in various rodent models of hypertension (e.g. Dahl SS and SHR, 11-15) and allow researchers to induce numerous factors of metabolic syndrome, including hypertriglyceridemia and insulin resistance at the same time (15, 16). Although Dahl SS rats fed high sucrose or fructose diets exhibit hypertension, it is not until a high level of NaCl (6%) is combined with high sucrose/fructose that there is an exacerbation of the hypertension (~10-15% higher) and a pronounced increase in mortality (Figure 1, 17, 18). Outbred rat strains such as the SD and Wistar rats, which are widely used for obesity research, can also develop numerous components of metabolic syndrome (hypertension, insulin resistance, and hypertriglyceridemia) on diets high in fructose (60%; 14, 19-22). High fructose alone normally doesn't cause obesity in SD or Wistar rats, but in some cases (20), rats fed a purified high fructose diet may be heavier than those fed a GB diet in the same study. However, given the multitude of nutrient and non-nutrient differences between these two diet types (explained in later section), it is necessary to choose appropriate purified ingredient control diets to make more definitive conclusions regarding different nutrients and their effect on phenotype (2). In this case, a proper control diet would use a carbohydrate source such as corn starch, which contains glucose polymers only so that the only difference is the carbohydrate source.

The SHR is another well studied animal model of essential (or primary) hypertension, and is used to study cardiovascular disease. The SHR develops hypertension spontaneously with increases in blood pressure beginning early in life (5-6 weeks; 23). The peripheral resistance and typical cardiac output exhibited by the SHR are similar to human hypertension (24). Although SHR rats develop hypertension when fed a GB diet, which typically contains around 0.7-1% NaCl, increasing vascular resistance by adding ~7% NaCl to the same diet and/or by offering a saline solution of 1% NaCl further exacerbates the hypertensive phenotype (25, 26). Another genetic model is the Spontaneously Hypertensive Obese Rat (SHROB). Compared to SHR, SHROB rats develop higher systolic blood pressure under the influence of a high NaCl diet (27). After thirteen weeks of high dietary NaCl (4% in diet and 1% in water), these rats developed vascular pathologies closely resembling malignant hypertension (i.e. extremely high and life threatening) in human patients. Other models include the Obesity Prone (OP-CD) rat and the ZDSD rat, which both exhibit symptoms of hypertension and metabolic syndrome.

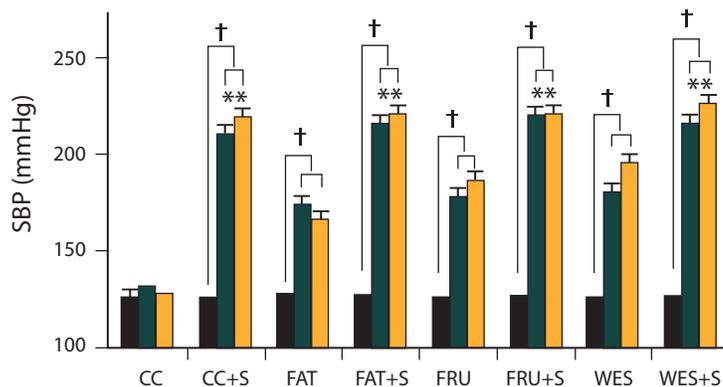


FIGURE 1. Systolic blood pressure (SBP) measured by tail-cuff method. Black bars represent pretreatment, green bars represent 5 weeks of treatment, orange bars represent 11 weeks of diet. DIETS: (CC)= complex carbohydrate, (CC+S)= complex carbohydrate + NaCl (FAT)= high fat, (FAT+S)= high fat + NaCl, (FRU)= high fructose, (FRU+S)= high fructose + NaCl, (WES)= western diet, (WES+S)= western diet + NaCl. Data are the mean \pm SEM. *P < .05 compared to the same dietary group with low salt at 5 and 11 weeks. †P < .05 compared to baseline measurement. Graphic representation - for details see reference (15).



Mouse

The mouse is not widely used as a model of diet-induced hypertension. Inbred mice such as those in the C57BL/6 strain can develop elevated blood pressure on purified ingredient diets high in NaCl (8%) relative to a GB diet, though the time frame for this appears to be in the order of several months (28). The NaCl sensitivity of blood pressure has been described in a number of knockout mouse models (e.g. Uroguanylin knockout animals; 29), but the long-term effects of excess NaCl do not appear to have been well investigated in wild-type mice. Switching to an 8% GB NaCl diet in 3-month-old male C57Bl/6J mice caused the mean arterial pressure level to increase by 6 mm Hg after only 2 days. However, no further increase occurred following 6 or 14 week period on the 8% NaCl diet (30-32).

Compared to a purified ingredient diet with low levels of fat (i.e. 10-15 kcal% fat), high-fat diets (i.e. 45-60 kcal% fat) have also been fed to C57BL/6 mice, with or without high levels of NaCl, to see whether metabolic disorders (i.e. increased adiposity, glucose intolerance) normally observed after high fat feeding are also associated with increased blood pressure. In one such study, a purified ingredient diet with 60 kcal% fat (mainly lard as fat) was found to elevate mean arterial pressure after only 7 days relative to a matched purified low fat diet (around 3 mm Hg). Adding ~5% NaCl to the diet further increased blood pressure, but only resulted in a further increase of 2.1 mm Hg relative to the low fat diet with similar NaCl levels (33). The major observation was reduced sodium excretion in animals fed a high fat diet compared to those fed a low fat diet, but unlike humans with metabolic syndrome, it was not related to increased renal sodium reabsorption due to aldosterone.

Other Factors That Can Influence Diet-Induced Hypertensive Phenotype

Grain-Based (GB) Diets vs Purified Diets

The type of diet and its effect on development of the hypertensive phenotype is an important factor that needs to be considered. GB diets and purified ingredient diets are very different, and likely account for some of the differences observed in hypertensive responses between rodents fed these diets. For example, GB diets typically contain phytoestrogens and heavy metals such as arsenic while these are typically absent in purified ingredient diets. Furthermore, fiber levels in GB diets are high and come from multiple grain sources, which is very different from typical purified ingredient diets which contain lower levels of fiber as mainly cellulose (2). Given that purified ingredients are more refined without the potential 'noise' from these factors, and are easy to modify, they provide a distinct advantage to those interested in studying hypertension in a controlled and deliberate way.

An example of how these two diet types compare for diet-induced hypertension is found in a study by Mattson et al. When 4% NaCl was added to both a GB diet and a purified ingredient diet, Dahl SS rats fed the purified ingredient diet had higher blood pressure and more renal damage compared to GB diet fed rats (34). One potential reason may be due to differential regulation of vascular nitric oxide synthase (NOS) function when fed a purified ingredient vs GB diet. When 16 week old rats weaned on the purified AIN-76A diet were switched to GB diet, the animals had a loss of NOS-mediated vasorelaxation in third-order mesenteric arteries – this could favor greater vasoconstriction and may lead to increased risk of vascular disease (35). Of equal interest is the finding that offspring from dams who were fed the 4% NaCl purified ingredient diet (relative to GB diet) had higher blood pressure regardless of the diet they were fed after weaning (34). In another study, hypertension and renal injury induced by a 4% NaCl diet (AIN-76A based) were substantially attenuated in Dahl SS/Crl rats that had been maintained for many generations on the GB diet compared to Dahl SS/Mcw rats maintained on the purified AIN-76A diet (36). Sodium levels are likely not the sole reason, considering that typical purified ingredient diets contain about 0.1% Na (~0.3% NaCl), while GB diets contain about



0.3-0.4% Na (0.75-1% NaCl) and typically higher levels (around 1.6% Na) elevate blood pressure in Dahl SS rats. GB diets and purified diets also differ in the levels of minerals (such as sodium and potassium), protein sources (see next section), presence or absence of phytochemicals, carbohydrate type, and/or the level and type of fiber (2). Given the differential response to these two types of diets, a concerning fact is that the two most popular commercial suppliers of Dahl SS rats do not use the same commercially available diet to maintain their Dahl SS colonies. Thus, the researcher needs to be aware of what diets their animals are being fed by the animal vendor as this could influence future phenotype in their study.

Protein

Soy protein (a common protein source in GB diets) has been shown to attenuate the development of hypertension in the SHR model in comparison to diets containing casein (37). Soy protein is known to contain the phytoestrogen genistein (and others), and these compounds attenuate NaCl-induced hypertension (38, 39). Given that GB diets typically contain soybean meal and that purified ingredient diets use only casein as the protein source, this could contribute to the differential effects of diet type on blood pressure regulation (34). In another study, replacement of casein with wheat gluten in male SS/Mcw rats significantly reduced body weight, mean arterial pressure, and albumin excretion (40). In addition to the type of protein, the level of protein was also found to have an effect, as restriction of protein intake protected Dahl SS rats from hypertension and kidney disease (41).

Gut Bacteria

A study published in 2015 showed that the Dahl SS rat had a distinct gut bacterial profile compared to the Dahl SR rat (i.e. those which are salt resistant) (42). In additional experiments, these animals were administered antibiotics for ablation of microbiota and Dahl SS and SR rats were then transplanted with either Dahl SS or Dahl SR rat cecal contents. In contrast to other studies where transplant receiving animals typically take on a similar phenotype as their donors, systolic blood pressure of Dahl SS rats given a single bolus of cecal content from Dahl SR rats was elevated and lifespan was reduced in comparison with those same rats given Dahl SS rat cecal content. These data demonstrate a clear link between gut microbes and blood pressure regulation. Because of this unexpected outcome, it is necessary to further examine how host genome and microbiome interact in the context of hypertension in the Dahl rats, using properly controlled diets.

Attenuation of Hypertension by Certain Nutrients

The nutrient profile of purified ingredient diets can be easily modified to study strategies to reduce blood pressure in hypertension models via diet. For example, hypertension resulting from feeding an 8% NaCl diet can be prevented by supplementing the diet with extra potassium. Dahl SS rats consuming diet with Na/K ratio = 1 had a mean systolic blood pressure of 137.4 mm Hg as compared with 169.9 mm Hg for those fed a diet with a Na/K ratio = 10 (43). In addition, dietary supplementation with antioxidants (such as vitamins E and C) can lower blood pressure in the stroke-prone, SHR or the Dahl SS rat (44-46). Other than micronutrients, the type and level of protein being used, carbohydrate (starch vs sucrose/fructose) and fiber (47) can also contribute to attenuation of blood pressure in these models.

We have briefly covered some rodent models that can be used to study diet-induced hypertension. By using purified ingredient diets, it is possible to clearly define how nutrients affect the hypertension phenotype. As the specific goals and needs for each researcher will vary, the careful selection of the rodent strain, diet type and composition, and control diet are of immense importance in the development of a consistent and useful phenotype.



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