Hypertension

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Phenotypic Expression of Hypertension in Rodent Models through Dietary Manipulation

A Brief Review of the Scientific Literature- October 2008
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The pathogenesis of hypertension in humans is not fully understood. This disease of persistent elevation of blood pressure is a multifactorial combination of genetic and environmental factors. To better understand the specific mechanisms involved, as well as to research treatments for prevention of hypertension, various animal models have been developed to mimic the hypertensive responses seen in humans.

Historically, the preferred small animal model for hypertension research has been the rat. This may be due to the amount of published physiological data, relative small size, and robust responses seen in some genetic strains. Because of the polygenic nature of hypertension, numerous rat models have been developed including selective bred homozygous hypertensive rat strains (e.g. spontaneously hypertensive rat [SHR] and Dahl salt sensitive [Dahl SS]) and outbred strains (e.g. Sprague Dawley) to elucidate the desired hypertensive phenotype. As the form of hypertension can differ between strains, researchers need to not only be aware of the form of hypertension that the individual strain exhibits but also the impact that a particular type of diet may have on the phenotypic response.

Sodium Induced Hypertension

High sodium diets are commonly used to study diet induced hypertension, since increasing levels of circulating sodium cause cells to release water (due to osmotic pressure) which elevates the pressure on blood vessel walls.

Lewis Dahl developed, from selectively inbred Sprague Dawley rats, the Dahl salt-sensitive (Dahl SS) and Dahl salt-resistant (Dahl SR) rats based on their response to an 8% NaCl diet (1). Weaned Dahl SS can rapidly develop elevated blood pressure (>180 mm Hg) when fed an 8% NaCl diet in as little as 2 weeks for some individuals, though the average for the strain is usually closer to 4-6 weeks (1-4). When fed a lower levels of NaCl, hypertension along with vascular and renal lesions develop though the length of time is typically longer (5, 6). The age of the animal also seems to play a role in the development of salt induced hypertension. Dahl SS rats placed on a high salt diet (8%) at 3 or 6 months after weaning developed elevated blood pressure at a slower rate compared to those placed on the diet at weaning. None of the animals typically survive beyond 8 months on the diet regardless of the age at which they start (5). In contrast, the Dahl SR rat fails to exhibit elevated hypertension or vascular and renal lesions even after being placed on a high salt diet for several months (1, 6-8).

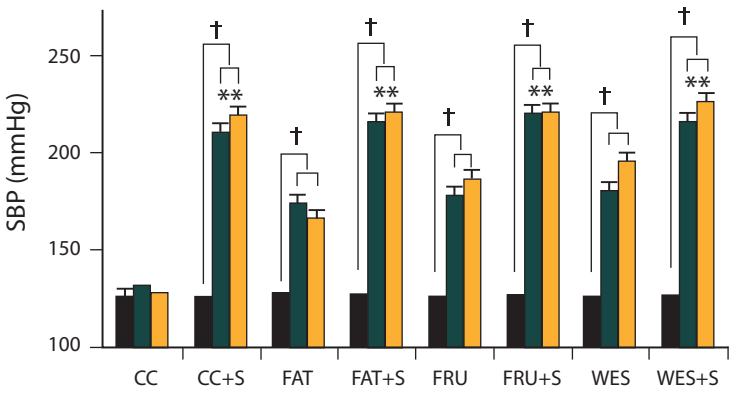

FIGURE 1. Systolic blood pressure (SBP) measured by tail–cuff method. Black bars represent pretreatment, green bars represent 5 weeks of treatment, orange bars represent 11 weeks of diet. DIETS: (CC)= complex carbohydrate, (CC+S)= complex carbohydrate + NaCl (FAT)= high fat, (FAT+S)= high fat + NaCl, (FRU)= high fructose, (FRU+S)= high fructose + NaCl, (WES)= western diet, (WES+S)= western diet + NaCl. Data are the mean ± 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 (25).

As the name implies the SHR develops hypertension spontaneously with increases in blood pressure beginning early in life (5-6 weeks) (9). As the peripheral resistance and normal cardiac output exhibited by the SHR are similar to human hypertension, this strain has been considered a good model of essential hypertension (10). Increasing the vascular resistance with the addition of NaCl (~7%) to the diet and/or saline solution of 1% NaCl provides an additive effect on increasing blood pressure in the SHR (11, 12).

As a model of diet-induced hypertension, the mouse is not widely used. Inbred mice such as the C57BL/6 can develop elevated blood pressure on purified diets high in NaCl (8%), though the time frame for this appears to be on the order of several months (13). Sequencing of the mouse genome coupled with the successful development of transgenic and knockout mouse lines allows researchers to investigate the roles that individual genes play within specific mechanisms of renal physiology under both normal and pathologic conditions (14).

Other Dietary Factors that can Influence the Hypertensive Phenotype

Dietary factors other than sodium can play a role in the degree and onset of hypertension in rodents. When 4% NaCl was added to both a chow diet and a purified ingredient diet, Dahl SS rats fed the purified diet had higher blood pressure and more renal damage compared to chow-fed rats (15). Of equal interest is the finding that offspring from parents who were fed the 4% NaCl purified diet had higher blood pressures regardless of the diet they were fed after weaning, suggesting that the diet fed to the mother during

pregnancy can promote hypertension in the offspring. How does the background diet (chow vs. purified) affect the outcome in this case? The reasons are not clear but may be related to fundamental differences between chows and purified diets in the levels of minerals such as sodium and potassium, protein sources, presence or absence of phytochemicals, carbohydrate type, and/or the level and type of fiber. Typical purified ingredient diets contain about 0.1% Na (0.25% NaCl), while chow diets contain about 0.3-0.4% Na (0.75-1.0% NaCl). Soy protein in chow based diets (a common protein source in chows) has been shown to attenuate the development of hypertension in the spontaneous hypertensive rat (SHR) in comparison to diets containing casein (the primary protein source used in purified diets) (16). Soy protein does contain the phytoestrogen, genistein, which has been shown to blunt the increase in blood pressure due to NaCl induced hypertension (17). As casein contains no phytoestrogens, the differences seen in blood pressure between animals fed chows and purified diets may be partially due to the variable levels of genistein and other phytoestrogens within chow (18).

Diets containing normal levels of NaCl but high in fructose or sucrose (around 60% of calories) can increase blood pressure in various rodent models (e.g. Dahl SS, SHR) of hypertension (19-23) and allow researchers to evaluate numerous factors of metabolic syndrome, including hypertriglyceridemia and insulin resistance (21, 22). Although Dahl rats fed high sucrose or fructose diets exhibit hypertension, it is not until a high level of salt (6%) is combined with high sucrose/fructose that there is an exacerbation of the hypertension and a pronounced increase in mortality (24, 25) FIG. 1. Outbred rats strains such as the Sprague-Dawley and Wistar rats (which are in widespread use for obesity research) can also develop numerous components of metabolic syndrome (hypertension, insulin resistance, and hypertriglyceridemia) on diets high in fructose (60%) (21, 26) as well as hypertension concurrent with the development of obesity (27-29).

As one might expect not only can one elevate blood pressure through dietary measures, but hypertension can be attenuated by way of the diet. Similar to findings in humans, hypertension resulting from feeding an 8% NaCl diet can be prevented by supplementing the diet with extra potassium (2, 30). Dietary supplementation with antioxidants (such as vitamins E and C) has been shown to lower blood pressure in the stroke-prone, SHR or the Dahl SS rat (31-33)Therefore, this suggests that low intake of these micro-nutrients could promote hypertension.

We have briefly covered some of the disease models that can be used to study diet induced hypertension. What should be clear is that while some dietary factors promote one phenotype (i.e. sodium induces hypertension), others may promote multiple phenotypes (high fructose diets to promote insulin resistance, hypertriglyceridemia, and hypertension). As the specific goals and needs for each researcher will vary, the careful selection and control of both the strain and diet are of immense importance in the development of a consistent and useful phenotype.

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