Hypertension

Phenotypic Expression of Hypertension in Rodent Models through Dietary Manipulation

_A Brief Review of the Scientific Literature_ October 2008
by Matthew Barker, M.S. Project Manager & Scientist, Research Diets, Inc.

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).

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...
Hypertension could promote hypertension. 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 sucrose (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.

References
3. Tian, N, Thrasher, KD, Gandy, PD, Hughson, MD, Manning, RD, Jr.: Antioxidant treatment prevents renal damage and dysfunction and reduces arterial pressure in salt-sensitive hypertension. Hypertension 45:934-939, 2005
Custom OpenSource Diets
Research Diets, Inc has pioneered the formulation and production of diet leading to hypertension in laboratory animals. Our scientists specialize in providing custom purified OpenSource diets. By carefully designing the diet formula to fit your protocol, you have complete control over small or large changes in diet composition. Please use a dietary supplement report what your animals were fed, repeat the formula and revise diet composition as necessary.

Incorporating Test Compounds
Research Diets, Inc. will incorporate your test compound into pelleted diets for simple, safe dosing. Feeding test compounds eliminates dosing related stress to the animal, eliminates vehicle effects, and saves time and labor. Consult with one of our scientists on the formula, determine the dosage required and the diet will be produced and shipped in 5 to 7 business days.

Value Added Resource
The value of our products is in the scientific support we provide. Our Resource Center is staffed with Masters and Ph.D. level scientists with access to over 14,000 original formulas and a database of more than 3,800 journal articles. We welcome the opportunity to talk science with researchers throughout the world as we maintain our leadership role as the knowledge base for OpenSource Diet formulation.

BioDAQ Episodic Intake Monitor
BioDAQ E2 Episodic monitoring system measures the ad libitum food and water intake behavior of singly housed laboratory rats and mice at very high resolution in their home cage. Computer controlled electronics record food and water intake episodically by measuring the moment-to-moment, undisturbed intake behavior of the animals being studied. The animal’s behavior defines the variable period for these intake measurements through their native behavior.