Maternal involvement in the development of cardiovascular phenotype

R. McCarty, M. A. Cierpial*, C. A. Murphy*, J. H. Lee* and C. Fields-Okotcha

Department of Psychology, University of Virginia, Charlottesville (Virginia 22903-2477, USA)

Abstract. Over the past 20 years, laboratory studies of genetically defined animal models of human essential hypertension have provided valuable information on the pathophysiology of this disturbance in cardiovascular regulation. Relatively fewer studies have examined the impact of preweaning factors on the developing cardiovascular system of hypertensive animals. In our laboratory studies, we have utilized two inbred genetically hypertensive models: the spontaneously hypertensive (SHR) rat and its Wistar/Kyoto (WKY) normotensive control strain as well as the Dahl hypertension-sensitive (SS/Jr) and hypertension-resistant (SR/Jr) strains. To manipulate the preweaning maternal environment, we have employed the technique of reciprocal cross-fostering of litters between hypertensive and matched normotensive mothers. Our findings to date point to the maternal environment as a powerful influence on the development of high blood pressure in genetically hypertensive rats. In general, hypertensive rats reared by normotensive foster mothers have significant reductions in arterial blood pressure in adulthood. Thus, the progression of hypertensive disease is not strictly predetermined by genotypic factors. Rather, a genetic predisposition to hypertension interacts with preweaning environmental factors to determine an animal's cardiovascular phenotype in adulthood.

Key words. Cardiovascular phenotype; animal model; genetic hypertension; SHR; maternal behavior; cross-fostering.

Introduction

Diseases of cardiovascular regulation make a significant contribution to morbidity and mortality in the majority of developed countries of the world[55]. In particular, biomedical researchers have for the past 3 decades devoted considerable effort to determining the pathophysiological mechanisms responsible for the development and maintenance of elevations in arterial pressure. Recently, concern has been expressed for the deleterious effects of blood pressure elevations in young children and adolescents[3, 27, 35, 68, 70]. The results of several long-term epidemiological studies indicate that one approach to reducing cardiovascular disease in adults is to implement at an early age aggressive treatments to reduce risk factors linked to the development of hypertension[4, 5, 9].

In studies with young children, several variables have been shown to exert a significant influence on blood pressure development. These include race, gender, body size and family history[5, 27, 43, 70]. Additionally, elevated blood pressures that are detected early in life tend to be maintained into young adulthood unless treatment regimens are instituted. At present, the consensus is that essential hypertension begins early in life and that some end organ damage may result in those children with systolic blood pressures in the top decile compared to age-matched peers[29, 35].

To examine the developmental course of essential hypertension in humans from infancy to middle age, one would need to marshall considerable resources to allow repeated measures of blood pressure and related physiological and behavioral variables.

Another avenue for examining the complex etiology of human essential hypertension is to investigate the early onset and later maintenance of high blood pressure in genetically selected laboratory animals[7, 44, 72, 73]. Modelling developmental processes related to essential hypertension in laboratory animals presents a number of advantages over life span developmental studies of human hypertensives. These include a greatly shortened life span, especially in laboratory rodents, the availability of genetically defined populations, and an ability to employ invasive procedures to investigate mechanisms of blood pressure regulation in normotensive and genetically or experimentally hypertensive animals.

Beginning in the 1960s, several small rodent models of essential hypertension were developed and made available to biomedical researchers throughout the world. Since that time, a great many investigations have been published that relate to pathophysiological changes which attend the appearance of established hypertension in several different animal models[28, 45, 56, 60]. However, ontogenetic studies of blood pressure regulation in the various animal models have received relatively little critical attention.

We have several goals for the remainder of this paper. First, we will present information relating to the characteristics of two animal models of essential hypertension that have been utilized by us and many others. Next, we will summarize recent studies from our laboratory relating to maternal influences on the development of genetic hypertension. Finally, we will conclude by presenting our thoughts on the concept of the cardiovascular phenotype as it relates to the dynamic interplay between early environmental influences and inherited susceptibility to cardiovascular disease.

Animal models of essential hypertension

Background. Beginning in the 1950s, several laboratories set out to develop small rodent models of essential hyper-

tension using selective breeding techniques. In general, breeding colonies of laboratory rats were screened for basal systolic blood pressures by tail cuff plethysmography or for pressor responses to dietary salt loading. Those adult male and female rats with higher than normal systolic blood pressures or with significant pressor responses following salt loading were mated over many generations. Similar mating protocols were followed for male and female rats that had normal resting blood pressures or a blunted pressor response to salt loading. The end result of several such efforts was the development of inbred strains of genetically hypertensive and matched normotensive strains of laboratory rats. These include the New Zealand [63], Lyon [22], Milan [6], Kyoto [57] and Dahl strains [82]. Our focus for the remainder of this paper will be directed at the Kyoto and Dahl strains of hypertensive rats.

The spontaneously hypertensive rat. The spontaneously hypertensive (SHR) rat and its Wistar-Kyoto (WKY) normotensive control were developed in 1963 by Okamoto and Aoki at Kyoto University in Japan [57]. The foundation stock for the SHR strain was a breeding colony of Wistar rats. Unfortunately, the WKY strain was not established as an inbred strain until several years after the SHR strain was carried through 20 generations of brother-sister mating. This methodological flaw has presented major difficulties over the years relating to having a suitable normotensive control for studies with the SHR [37]. SHR and WKY rats were made available to laboratories throughout the world beginning in the late 1960s. Since that time, a voluminous literature has developed which describes various neural, humoral, physiological, molecular and anatomical changes that precede, attend or result from the development of hypertension in SHRs [45, 60]. In contrast, relatively little attention has been devoted to studies of preweaning SHRs when blood pressures are only slightly greater than age-matched WKYs [31, 32].

In SHRs, systolic blood pressures remain within the normotensive range ($\leq$ 150 mm Hg) until approximately 10 weeks of age. It is important to note, however, that blood pressures of SHRs are consistently greater than blood pressures of age-matched WKYs as early as the day after birth [8, 30, 39]. Indeed, several investigators have described structural changes in the cardiovascular system of SHRs as early as the first week of postnatal life [16, 41, 61, 69]. Specifically, Azar and co-workers [2] detected cardiac hypertrophy in SHRs in utero. Because of the very early divergence in blood pressures and structural alterations in the cardiovascular system of SHRs, we have emphasized the value of investigations with preweaning SHRs to provide a more complete understanding of the etiology of this model of genetic hypertension [49].

The Dahl hypertensive rat. Another rodent model of hypertension was developed in the laboratory of Professor Lewis K. Dahl during the early 1960s. Dahl's special area of interest was the relationship between dietary sodium intake and the development of hypertension. As an approach to attacking this problem, Dahl and his co-workers developed two lines of Sprague-Dawley laboratory rats [17, 36]. The Dahl salt-sensitive (DS) line developed hypertension when fed a diet containing high concentrations of sodium chloride (usually 8% NaCl). Rats of the Dahl salt-resistant (DR) strain had blood pressures within the normotensive range when fed control or 8% NaCl diets. Dahl never carried these lines beyond 5-6 generations of brother-sister mating because resting blood pressures of DS rats gradually increased above levels for DR rats. Because the lines were not carried through to 20 generations of brother-sister mating, blood pressures of rats of the two lines on control or 8% NaCl diets were not always consistent. In some instances, DS rats were hypertensive without salt loading while in others DR rats exhibited increases in blood pressure in response to salt loading.

In response to these problems, Professor John Rapp of the Medical College of Ohio initiated a program of brother-sister matings of DS and DR rats from Dahl's laboratory for more than 20 generations. This multi-year effort resulted in the development of two inbred rat strains: the SR/Jr is normotensive and unresponsive to an 8% NaCl diet while the SS/Jr rats are as high as 200 mm Hg by 12 weeks of age, and rats of this strain often die by 20 weeks of age due to renal or cerebrovascular lesions. Although the inbred strains of Dahl rats have been available from commercial suppliers for the past several years, very few studies have utilized preweaning SS/Jr rats to examine initiating factors which contribute to the age-related increases in arterial blood pressure in this model of genetic hypertension [58, 59].

Preweaning influences on the development of genetic hypertension

Overview. Over the past 6 years, we have examined the contribution of preweaning factors to the development of hypertension in SHR and SS/Jr rats. In this program of research, our working assumption has been that the development of hypertension in SHRs and SS/Jrs represents a dynamic interplay between genotypic factors and specific aspects of the preweaning environment. In formulating this epigenetic view, we reasoned that several major blood pressure regulatory systems undergo extensive postnatal development in laboratory rats. These include the sympathetic-adrenal medullary system, the renin-angiotensin-aldosterone system, the parasympathetic nervous system and the baroreceptor system [49, 50]. We felt that specific environmental stimuli could modify the expression of inherited patterns of arterial hypertension by their effects on one or more of these blood pressure regulatory systems during the preweaning period. The lactating mother provides developing rat pups with a plethora of stimuli during the time between birth and weaning, including tactile stimulation, heat exchange,

nutrients, and olfactory cues. To modify maternal stimuli, we developed a cross-fostering paradigm whereby litters were exchanged between hypertensive and normotensive mothers. In our initial studies[11,13], hypertensive and normotensive litters were reared by the natural mothers (control litters), fostered to mothers of the same strain (in-fostered litters), or cross-fostered to mothers of the opposite strain (cross-fostered litters). All litters were culled to 8 pups on the day after birth (postnatal day 1) and exchanges of litters between mothers were completed no later than postnatal day 2. SHR and WKY litters were weaned at 21 days of age while SS/Jr and SR/Jr litters were weaned at 30 days of age. Male rats of each strain-treatment combination were group-housed from weaning until adulthood under standard conditions. Basal values of mean arterial pressure (MAP, mm Hg) and heart rate (HR, beats per min) were recorded in conscious, freely behaving adult rats via chronic tail artery catheters as described in detail by Chiueh and Kopin[10]. Summarized below are the results of 5 experiments in which we utilized the cross-fostering paradigm to examine maternal influences on blood pressure development in genetically hypertensive and normotensive rats. In each experiment, only one animal from each litter was included in each treatment group. The findings from these experiments have revealed that the preweaning maternal environment plays an important role in the development of hypertension in rats of the SHR and SS/Jr strains.

Experiments. In our first set of experiments[11,13], we measured basal MAPs and HRs in control, in-fostered and cross-fostered SHRs and WKYs at 120 days of age. MAPs of control SHRs were in the hypertensive range and were significantly greater than values for control WKYs ($p < 0.001$). In both strains, MAPs of in-fostered rats were comparable to values for controls reared by the natural mother. MAPs of cross-fostered SHRs were significantly lower than corresponding values for control and in-fostered SHRs ($p < 0.001$). In contrast, cross-fostering did not affect blood pressures of WKYs (fig. 1). Resting heart rates of SHRs were significantly higher than for WKYs ($p < 0.001$). Basal heart rates were similar across treatment groups in SHRs. For WKYs, basal heart rates of in-fostered rats were lower than for cross-fostered rats ($p < 0.001$).

These findings revealed that blood pressure development in SHRs was affected by the preweaning maternal environment. In contrast, the cardiovascular system of WKYs appeared to be buffered against any blood pressure-elevating effects of the SHR maternal environment. In this experiment[51], we sought to extend our initial findings with the SHR and WKY strains to a different model of genetic hypertension. We utilized SS/Jr and SR/Jr breeding stock originally provided to us by Dr John Rapp. Basal values of MAP and HR were measured in control, in-fostered and cross-fostered rats of the two strains at 100 days of age. We selected an earlier endpoint

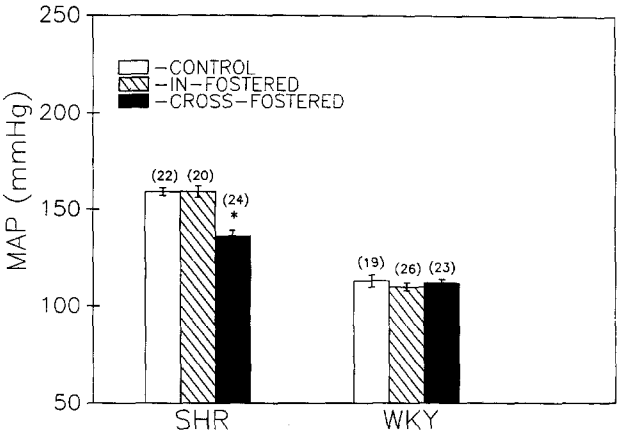

Figure 1. Resting mean arterial pressures (MAP, mm Hg) at 120 days of age for SHR and WKY male rats reared under control conditions, in-fostered to mothers of the same strain, or cross-fostered to mothers of the opposite strain. Data are presented as means ± SEM and sample sizes are indicated in parentheses. *$p < 0.001$ compared to control and in-fostered SHRs. Results are taken from studies by Cierpial and McCarty[13] and Cierpial, Konarska and McCarty[11].

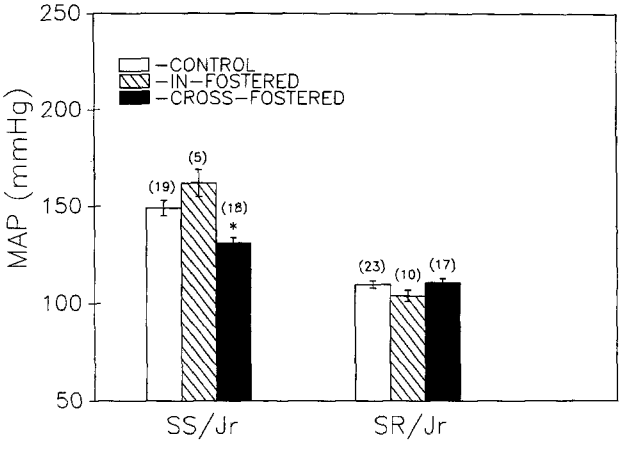

Figure 2. Resting mean arterial pressures (MAP, mm Hg) at 100 days of age for SS/Jr and SR/Jr male rats reared under control conditions, in-fostered to mothers of the same strain, or cross-fostered to mothers of the opposite strain. Data are presented as means ± SEM and sample sizes are indicated in parentheses. *$p < 0.01$ compared to control and in-fostered SS/Jr. Results are taken from a study by Murphy and McCarty[51] and unpublished results from our laboratory.

for this experiment than in our work with the SHR strain because SS/Jr rats begin to die from complications of hypertensive disease beginning about 100 days of age. Throughout the experiment, rats of both strains were fed a standard laboratory chow diet (approximately 0.7% NaCl).

As expected, basal MAPs of SS/Jrs were significantly greater than values for SR/Jrs ($p < 0.001$). We also found that cross-fostered SS/Jrs had significant reductions in basal MAPs compared to control or in-fostered SS/Jrs ($p < 0.001$). In contrast, cross-fostering did not affect adult blood pressures of Sr/Jr rats (fig. 2). Resting heart rates of SS/Jrs and SR/Jr rats were comparable at 100 days of age. In addition, resting heart rates in rats of both strains were not altered by foster-rearing.

These results with the inbred Dahl strains extended our findings in experiment 1 with the SHR and WKY strains. A consistent picture has emerged from these two experiments in which genetically hypertensive rats exhibited significant reductions in basal blood pressures in adulthood if they were reared from birth to weaning by a normotensive mother.

Next, we considered the possibility that the blood pressure-reducing effect of cross-fostering was limited to hypertensive litters reared by their companion genetically normotensive foster mothers. To address this issue, we examined basal MAPs and HRs in 18–20-week-old SHR and WKY rats that were reared by normotensive Sprague-Dawley (S-D) foster mothers[14]. Blood pressures of SHRs were significantly higher than those of either WKYs or S-Ds ($p < 0.001$). In addition, SHRs reared by S-D foster mothers had significant reductions in adult MAPs compared to naturally reared controls ($p < 0.001$). The magnitude of the decrease in MAP (26 mm Hg) was quite similar to the decrease in MAP reported in experiment 1 (23 mm Hg). Adult MAPs did not differ between control WKYs and those reared by S-D foster mothers. Similarly, MAPs of S-D rats were comparable in adulthood regardless of rearing condition (fig. 3).

Heart rates of adult SHRs were significantly higher than heart rates of adult WKY or S-D rats ($p < 0.05$). Rearing condition did not affect HRs for SHRs or WKYs. However, basal HRs of S-D rats reared by WKY foster mothers were lower than those of control S-Ds and of S-Ds reared by SHR foster mothers ($p < 0.05$).

Our findings in this experiment demonstrated that the same blood pressure lowering effects of cross-fostering reported above for SHRs reared by WKY mothers can also be obtained by employing normotensive S-D mothers in the fostering procedure. In this instance, the strain of the normotensive foster mother was unrelated to the Wistar-derived SHR. Given that the magnitude of the reduction in adult MAPs of SHRs reared by WKY or S-D mothers was similar, it would appear that the hypertensive maternal environment includes a factor(s) that are not present in the two types of normotensive maternal environments. Alternatively, WKY and S-D pups may be resistant to the hypertension-promoting effects of the SHR maternal environment.

An unresolved issue from the first three experiments relates to the time during the preweaning period when the maternal environment exerts its impact on the development of hypertension. We considered three possible outcomes:

1. The maternal effect is cumulative. That is, the longer the hypertensive pup remains with the normotensive litter, the greater the reduction in adult blood pressure.
2. The maternal effect is limited to a specific phase during the preweaning period.
3. A threshold amount of contact with the foster mother is required during any portion of the preweaning period.

In this experiment, there were six groups of SHR controls reared by the natural mother and individuals that were cross-fostered to WKY foster mothers for postnatal days 1–7, 8–21, 1–14, 15–21 or 1–21. We also included a group of control WKYs for purposes of comparison.

Our findings were generally consistent with outcome 2 described above. That is, SHRs reared by WKY foster mothers for either of the first two weeks of postnatal life had reductions in adult MAPs that were comparable to reductions noted for SHRs that were cross-fostered for the entire 3 weeks of the preweaning period. Basal HRs of SHRs were unaffected by foster-rearing (refer to the table).

In this study, we found that the timing of the cross-fostering effect corresponds well with the time when rat pups are maximally dependent upon the mother for nutrients. This is also the time when various blood pressure regulatory systems are undergoing substantial increases in functional capacity. Our working hypothesis at this point is that characteristics associated with mother-pup inter-

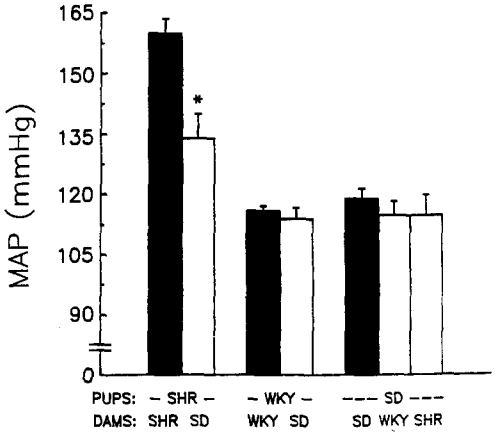

Figure 3. Resting mean arterial pressures (MAP, mm Hg) at 18–20 weeks of age for SHR, WKY and S-D male rats reared under control conditions or cross-fostered to mothers of the opposite strains. Data are presented as means + 1 SEM for groups of 7–10 rats. Results are from a study by Cierpial and McCarty[14].

Basal values for mean arterial pressure (mm Hg) and heart rate (beats per min) in control and cross-fostered (xf) SHRs and in control WKYs at 100 days of age

Strain/treatment (N)	Mean arterial pressure	Heart rate
SHR control (8)	152 ± 4	332 ± 11
SHR xf 1–21 (6)	124 ± 3*	331 ± 9
SHR xf 1–7 (6)	121 ± 7*	328 ± 14
SHR xf 8–21 (6)	126 ± 6*	320 ± 6
SHR xf 1–14 (6)	124 ± 4*	315 ± 7
SHR xf 15–21 (7)	154 ± 5	330 ± 8
WKY control (8)	111 ± 4	328 ± 10

Values are means ± SEM for the indicated numbers of rats per group.
* $p < 0.05$ (two-tailed t-test) compared to SHR controls.
Unpublished data from the authors' laboratory.

action (i.e. behavioral, nutritional, physiological) during the first two weeks of postnatal life are responsible for the blood pressure lowering effect of cross-fostering.

In the final experiment of this series[52], we tested the hypothesis that the preweaning environments of SHR and SS/Jr mothers would support the development of hypertension in pups of the opposite hypertensive strain. Although the SHR and SS/Jr strains were developed from different foundation strains and apparently have somewhat different etiologies, it is conceivable that the maternal environments provided by mothers of the two strains have characteristics in common. Six groups of rats were included in this study: 4 control-reared groups (SHR, WKY, SS/Jr and SR/Jr) and two cross-fostered groups (SHRs reared by SS/Jr foster mothers and SS/Jrs reared by SHR foster mothers). To maintain consistency across groups, all pups were weaned at 30 days of age. Direct measures of MAP and HR were obtained from each animal at approximately 100 days of age.

As expected, basal MAPs of SHRs were significantly higher than those of WKY controls ($p < 0.001$). In addition, blood pressures of SS/Jr rats were significantly greater than values for SR/Jr controls ($p < 0.001$). Interestingly, basal MAPs of cross-fostered SHR and SS/Jr rats were similar to their matched controls that were reared by the natural mothers (fig. 4). Basal heart rates of hypertensive rats were higher than values for their normotensive controls ($p < 0.01$). In addition, cross-fostering did not affect resting HRs in rats of the two hypertensive strains.

These findings suggest that the maternal environments provided by SHR and S/Jr mothers include some shared hypertensinogenic components. These shared characteristics appear to be sufficient to promote the full development of hypertension in pups of either strain.

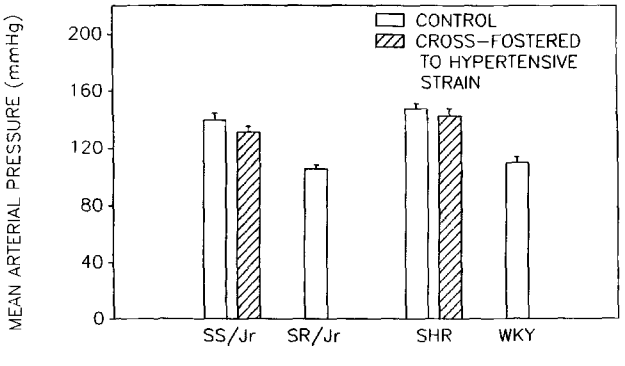

Figure 4. Resting mean arterial pressures (mm Hg) at 100 days of age for SHR, WKY, SS/Jr and SR/Jr male rats reared under control conditions. In addition, males from SS/Jr and SHR litters that were reciprocally cross-fostered soon after birth were also studied. Data are presented as means + 1 SEM for groups of 7–10 rats. Results are from a study by Murphy, Fields-Okotcha and McCarty[52].

Conclusions

Cross-fostering and the development of hypertension. The data presented from these five experiments on the Kyoto and the Dahl models of essential hypertension highlight the importance of the preweaning environment in the eventual development of high blood pressure in rats of these strains. Interestingly, the SHR and SS/Jr strains were developed from different breeding stock (Wistar and Sprague-Dawley, respectively) and present very different pathophysiological profiles. Yet, in each strain, our findings revealed that hypertensive pups reared by normotensive foster mothers had significant reductions in adult blood pressures. In contrast, hypertensive pups reared by hypertensive foster mothers did not exhibit any alterations in adult blood pressures. The reductions in arterial pressures of cross-fostered hypertensive animals appeared to be permanent and were not a result of a delay in the development of hypertension.

Other investigators have made use of the cross-fostering paradigm to investigate the role of preweaning factors in the development of hypertension. Consistent with our findings, DiNicolantonio and co-workers[20] reported systolic blood pressures at 12 weeks of age were reduced by approximately 30 mm Hg in SHR rats that were reared from birth to weaning by Sprague-Dawley foster mothers. In contrast, adult blood pressures of Sprague-Dawley rats reared by SHR foster mothers were similar to controls reared by their natural mothers. Azar and Hrushesky[1] also reported that SHRs cross-fostered to WKY mothers at birth exhibited reductions in blood pressures in adulthood compared to SHRs reared by their natural mothers. Finally, Woodworth and colleagues reported that the type of maternal environment affected cardiovascular reactivity in borderline hypertensive rats (BHR), the F_1 hybrids that result from crossing SHRs and WKYs. BHRs reared by SHR mothers responded with maximal pressor responses to a mild stressor (transfer to a novel environment) and maintained this maximal pressor response for up to 5 min after exposure to a more intense stressor (intermittent footshock). In contrast, WKY-reared BHRs responded with graded pressor responses to transfer and footshock and had greater reductions in heart rate 5 min after termination of footshock compared to BHRs reared by SHR mothers[71].

A cross-fostering experiment with SS/Jr and SR/Jr rats has also been conducted recently[18]. SS/Jr and SR/Jr litters were cross-fostered on the day of birth such that half of each litter was fostered to a mother of the opposite strain and the other half remained with the natural mother. Pups were weaned at 30 days of age and, 2 days later, were fed an 8% NaCl diet. Systolic blood pressures of adult SS/Jr and SR/Jr rats were not affected by cross-fostering. However, SS/Jrs reared by SR/Jr foster mothers displayed increased longevity compared to controls reared by their natural mothers. We have taken these

findings to indicate that SS/Jr are so responsive to salt loading that any beneficial effects of cross-fostering on blood pressures are masked by this dietary regimen. In our own work with these strains, we have provided rats with laboratory chow that contains 0.7% NaCl. In spite of the high salt diet employed by Dene and Rapp[18], cross-fostered SS/Jrs lived significantly longer than control SS/Jrs, confirming a beneficial effect of the normotensive maternal environment for this strain.

Maternal environment and blood pressure reduction: Putative mechanisms. A number of hypotheses have been advanced to account for the blood pressure lowering effects of cross-fostering in genetically hypertensive rats. These include strain differences in patterns of maternal care, in physiological responses to milk delivery to the pups, and in the quantity and quality of the milk. Recently, we examined patterns of maternal care in SHR and WKY mothers over the entire 21-day preweaning period, with observations made during the light and dark portions of the day-night cycle[15]. We found that SHR mothers were in contact with their pups more frequently, groomed their pups more frequently and assumed arched nursing postures over their pups more frequently compared to WKY mothers. Our findings were consistent with the suggestion that SHR mothers are more solicitous of their pups to compensate for their substantial delays in physical and behavioral maturation compared to WKYs[12].

Strain differences in cardiovascular responses to milk letdown may also play a role in the blood pressure reducing effects of cross-fostering. When rat pups receive milk ejections from their mothers, they exhibit rapid 30–50% increases in blood pressure as measured by indwelling carotid catheters[62]. The blood pressure responses to milk ejections from the mother or from a tongue cannula were significantly greater in SHR compared to WKY pups when tested at 15 days of age[54]. Myers and his co-workers have suggested that frequent feedings during infancy may actually promote the development of hypertension in genetically predisposed animals. Their suggestion fits well with our behavioral observations[15] and with those of Myers and his colleagues[53].

Finally, qualitative or quantitative differences in milk provided to developing pups could be involved in blood pressure development. Several reports have detected substantial differences in the concentration of milk electrolytes between SHR and WKY mothers[1, 20]. In particular, several laboratories have focussed on concentrations of sodium and calcium in the milk of hypertensive and normotensive mothers. Indeed, there is an impressive body of research to support links between increased dietary sodium and decreased dietary calcium as causal factors in the development of hypertension[22, 23, 34, 46, 48, 64]. To date, however, carefully controlled studies relating milk electrolytes to patterns of blood pressure development have not been conducted.

The hypertensive phenotype. Research from our laboratory has demonstrated clearly that the progression of hypertension is not strictly controlled by genetic factors present at conception. Rather, a genetic predisposition to hypertensive cardiovascular disease interacts with environmental factors during the life of the organism to determine its cardiovascular phenotype at any given time. We have emphasized that environmental factors present during the neonatal period may exert especially dramatic effects of the expression of the hypertensive phenotype that endure well into adulthood. These results argue for a substantial change in the conceptualization of hypertensive disease in laboratory animals and possibly in humans.

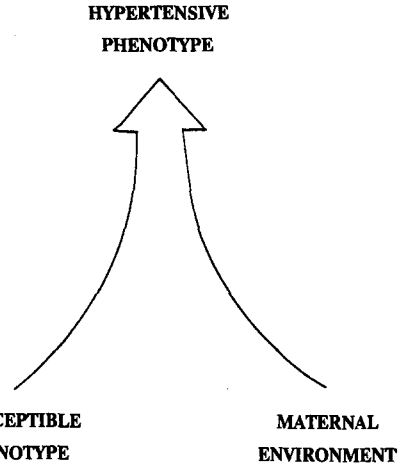

Figure 5. A susceptile genotype and an appropriate maternal environment interact to influence the development of the hypertensive phenotype.

In advancing the concept of a hypertensive phenotype, we have been influenced by the work of Desjardins and Lopez[19] on neuroendocrine phenotypes and by Surwit and colleagues[65] and Lehman and colleagues[42] on expression of the diabetic phenotype. In addition, earlier work by Dubos[21] on the role of early experiences in the later susceptibility to infectious diseases played an important role in guiding the studies presented here. Our results support the view that full expression of the hypertensive phenotype in SHRs and SS/Jrs requires a susceptible genotype and a hypertensive maternal environment. These findings extend the work of others relating to environmental influences on blood pressure development in SHRs[33, 38, 39, 66, 67, 74], in BHRs[40], and in Dahl hypertensive rats[25, 26]. A major challenge for this field of inquiry is to determine the mechanism by which early environmental stimuli act to modify the expression of the cardiovascular phenotype.

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* Present addresses: Mark A. Cierpial, Department of Psychiatry, Duke University Medical Center, Durham, North Carolina 27710, USA:, Carol A. Murphy, Department of Developmental Psychobiology, New York State Psychiatric Institute, 722 North 168th Street, Box 40, New York, New York 10032, USA; Jana H. Lee, Department of Psychiatry, The Johns Hopkins University School of Medicine, Baltimore, Maryland 21205, USA.

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Feeding in infancy: Short- and long-term effects on cardiovascular function

M. M. Myers, H. N. Shair and M. A. Hofer

Department of Psychiatry, Columbia College of Physicians and Surgeons, Columbia University and the New York State Psychiatric Institute, 722 West 168th St., New York (NY 10032, USA)

Abstract. Cardiovascular responses of adult organisms to feeding are well characterized and, in general, are understood as acute adaptations required for processing and distributing nutrients. Research over the past several years has shown that infants also have important cardiovascular responses to nutrient intake and that these are regulated by changes in autonomic activity to the heart and vasculature. Recent studies have provided results that suggest these responses in infancy may make an important contribution to the long-term development of cardiovascular function, in particular, adult blood pressure (BP). The purpose of this presentation will be to review the evidence that has led to this conclusion, offer ideas about how this potential early-life shaping of subsequent cardiovascular function may come about, and suggest further studies that will be required in order to characterize the mechanisms responsible for these effects.
Key words. Hypertension; infancy; genetic strains; environmental contributions.

Introduction

Beneath the seeming routine performance of behaviors required for ingestion of water and nutrients is an impressive array of physiologic mechanisms involved in processing this intake. The myriad changes in gastric motility and acid, bile, and hormone secretions which are required for digestion, absorption and cellular uptake of