Multi-author Reviews

Genetic models in brain and behavior research, Part IV

Nature/nurture and the nature of nurture in the etiology of hypertension

A. Blizard

Center for Developmental and Health Genetics, Pennsylvania State University, University Park (Pennsylvania 16802, USA)

Abstract. Four reviews on the the role of developmental factors in hypertension are introduced and set in historical context. Recent research in the laboratory rat has shown that the preweaning environment makes an important contribution to the level of blood-pressure reached in adult life in genetic models of hypertension. Both of the most commonly used models of hypertension, the SHR and SS/Jr rat strains, exhibit lower BP in adult life, if they are fostered shortly after birth to mothers from their normotensive control strains. It has been suggested that it is the idiosyncratic maternal behavior of the hypertensive mothers which contributes to the elevated BP of their offspring, and it has been amply demonstrated that there is an association between a constellation of behaviors emitted by rat mothers and the adult BP of their offspring in a wide variety of genetic groups (inbred hypertensive animals, F1's and F2's). In addition to the above, maternal environment has been demonstrated to have a significant impact on the pathophysiological response of hypertensive animals to a high salt diet. Being raised by an SHR mother, versus an SS/Jr mother, increases the magnitude of BP increases to a high salt diet, susceptibility to hemorrhagic stroke, body weight loss and the risk of mortality. A variety of physiological systems are undergoing rapid change during the preweaning period and may mediate the effects of differences in the maternal environment. These include the renin-angiotensin system and the peripheral sympathetic nervous system. Nutritional factors may be involved in all of the phenomena referred to above. Thus, any physiological mechanisms that are proposed to link maternal behavior to its effects on the physiology of adult animals should recognize the involvement of nutritional factors. Research on the role of developmental factors such as maternal behavior in genetic models of hypertension is at the interface of two growing disciplines: behavior genetics and developmental psychobiology. The methodological and conceptual contributions of these fields to advancing our understanding of these phenomena is emphasized.
Key words. Hypertension; SHR; SS/Jr; maternal environment; nutrition; early experience; pathophysiology; genetics.

Despite the oppositional nature of early debates concerning the contribution of nature (genetic variation) and nurture (environmental variation) to complex behavioral traits, it is now widely accepted that both genetic and environmental variations make a substantial contribution to phenotypic variation in many behavioral and physiological characters [20]. The present group of reviews, the 4th in the series entitled, Genetic Models in Brain and Behavior Research, deals with the contribution of genes and environment, particularly the behavioral environment, to the etiology of hypertension. They are focussed on rat models of hypertension which have been produced by selective breeding, a common procedure which concentrates the alleles underlying high and low expressions of a character conveniently within a given strain so that its genetic architecture, physiological correlates etc. can be conveniently studied. These models have become the standard experimental preparations for research on hypertension. Thus, the results discussed in the present reviews make contact with a huge body of literature emanating from many countries and are relevant to many of the central themes of hypertension research. Any reader unfamiliar with these genetic models will find a brief overview of the methods used to develop them in the review by McCarty et al.[17].

In the preceding paragraph, nurture was defined in very general terms as environmental variations affecting a character. However, nurture has special psychological connotations relating to the mother/infant dyad, and the significance of the latter has been the focus of the distinguished experimental contributions of one of the contributing authors [13]. In this review series, particular attention is given to the contribution of variations in mother/pup interactions to phenotypic variation in blood pressure (BP) in adult life in rat models of hypertension. The focus on maternal/infant interactions will not seem out of place to behaviorally-oriented researchers. Psychologists and psychiatrists habe been consistently preoccupied with the potential contribution of these interactions and other early experiences to psychophysiological function in adult life. Interest in this phase of existence was first stimulated by a variety of theoretical promptings as researchers sought to explore Freudian [14] or Hebbian [8] ideas by means of research with ro-

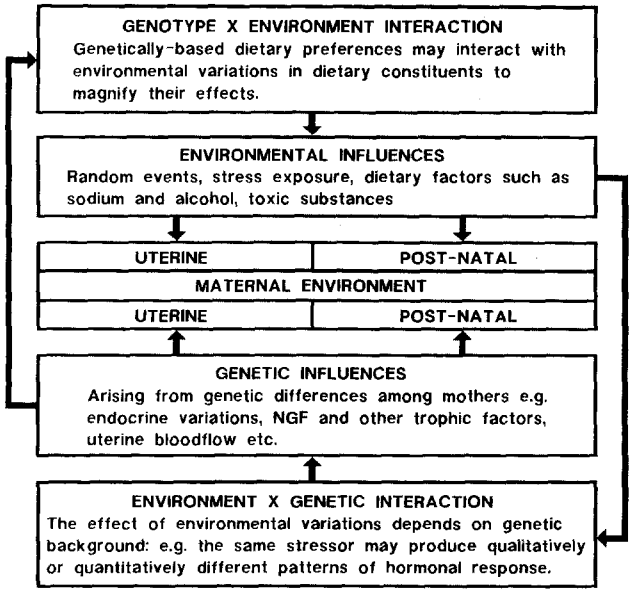
dents. Later, recognizing that, regardless of theoretical underpinnings, the period of early development was a time when many fundamentally important biological systems were rapidly changing, and, therefore, vulnerable to disruption, not only by variations in the mother/infant interaction, but also by other environmental interventions, early experience research underwent a major growth phase. In the late 50's, and in the decade of the 60's, researchers such as Victor Denenberg[9] and Seymour Levine[16] showed how neonatal manipulations of many kinds altered a variety of behaviors in adult life.

An intriguing aspect of this field, which is especially relevant to the present series of reviews, is that interest in the effects of early environmental manipulations has been largely confined to psychologists. Although it was apparent that manipulations of the neonate did affect physiological systems[2,10], few physiologists did active research in this area. Perhaps they already had enough disciplinary fish to fry, but there was also a bias, sometimes stated, but usually unstated, against studying the long-lasting effects of alterations in the early environment. In any case, the disciplinary confinement of early experience research undoubtedly hampered progress in developing an appropriate picture of the scope of systems affected by experimental manipulations of the early environment.

Aside from these preconceptions, there was dissatisfaction with this area of research, because it was difficult to specify the stimuli involved in the various aspects of the early environment which were studied. For example, the experimental manipulation known as 'early handling' (a procedure which involved removing neonates from their nest for a brief period of time for several days early in life) involved perturbations of many somatic systems. Inability to specify the salient independent variable in such manipulations made it hard to identify physiological pathways between neonatal treatment and later behavior. Other features of early experience studies which habe hampered progress in this field habe been previously discussed by Henderson[12].

The present set of articles make an important step toward re-focussing interest upon early experience and showing its longterm relevance to fundamental physiological processes. This has been accomplished by careful observation of maternal/infant interactions in early life, and use of innovative statistical methods to demonstrate the relationship between early experience and adult physiological function. For the most part, the authors of these studies are psychologists, but in order to make meaningful measurements of physiological processes in behaving animals, they have had to develop special physiological techniques in order to make measurements under appropriate behavioral conditons. The net result is that they habe been able to demonstrate that early experience makes a major contribution to the level of blood-pressure displayed by an animal in adult life. In the studies by McCarty and colleagues, being raised by a genetically hypertensive rat mother appears to account for a substantial proportion of the difference in BP between two models of genetic hypertension, the spontaneously hypertensive rat (SHR) and the inbred, salt-sensitive (SS/Jr) rat, and their respective normotensive controls[17]. Myers et al., using a different methodological approach, have shown, in a series of studies, that adult BP is correlated with variations in maternal behavior[19]. Furthermore, they have suggested that body weight, or rather weight gain during a specific period of development may be importantly associated with the effects of maternal behavior on adult BP. In the review by Blizard and Adams we extend the importance of maternal environment to pathophysiology by comparing the effect of being raised in utero and post-natally by SHR or SS/Jr mothers. In this comparison, being raised by an SHR mother greatly enhanced susceptibility to BP-elevations when hybrid animals were placed on high salt diet in early life, increased risk of suffering cerebral hemorrhage, body weight loss and early death[4]. Nutritional state, at least as indexed by body weight before placement on the high salt diet, was an important predictor of susceptibility to the adverse effects of placement on the high salt diet. The paper by Kirby and Johnson makes an important contribution toward identifying some of the physiological systems which are undergoing rapid development during the preweaning period, and which may be altered, either by variations in maternal behavior, or, by other developmental interventions[15].

In this group of reviews, there is much interest in the possibility that genetically-based variations in maternal behavior alter the environment of developing pups and influence offspring blood pressure in adult life. However, there is obviously a much wider range of stimuli capable of altering developmental processes which are worthy of study and these have been discussed elsewhere[3]. A categorization of some of the ways in which maternal influences may impact on the developing organism is summarized in the figure. In addition to genetic differences in maternal behavior, both random and systematic alterations of the environment obviously have the capability of acting directly, or indirectly (via their effects on the mother), on developing animals. Although the possible effects of such treatments on cardiovascular regulation in adult life are not discussed in the present reviews, it would obviously be valuable to investigate the effect of specific environmental perturbations in these hypertensive models. Gene environment interactions are extensively discussed in these reviews: in the figure, examples of two different kinds of interactions are depicted, those that occur when a stimulus is imposed on different genotypes and those that occur as a result of genotypes seeking out different environments. This distinction may be hard to make in practice but is useful in conceptualizing gene/environment interactions and in planning experiments to investigate them. Not shown, but discussed in these reviews, is the fact that the developing organism



Genetic and environmental influences during pre- and post/natal development.

also contributes to variations in the maternal environment and is itself a potential source of gene/environment interactions.

The reviews emphasize the non-additive nature of the interaction between genotype (nature) and environment (nurture) in the determination of BP in adult life. According to McCarty's results, genetic selection for high blood pressure in the SHR and SS/Jr models of hypertension has fixed genes within SHR and SS/Jr strains which impact on maternal/neonate interactions to alter BP in adult life. However, the alteration in the maternal environment does not impact on neonates regardless of their genotype. Being raised by SHR mothers has no effect on BP of normotensive WKY animals in adult life. Thus, there is an interaction between maternal environment and pup genotype when considering their contribution to an individual rat's BP in adult life. Stated plainly, in the context of the genetic variations which produce elevated BP in the SHR, to achieve the dubious distinction of having a BP well within the hypertensive range in adult life, requires that an individual possess both, alleles that predispose to moderate hypertension, and also, that an individual be raised by a hypertensive mother.

Within behavior genetics, the study of gene/environment interactions, i.e. the non-additive combination of genes and environmental manipulations, was pioneered by Henderson who showed their significance in influencing a variety of behaviors in adult life, and emphasized the importance of appropriate sampling of genotype and environment in understanding the genetic architecture and contribution of environment to phenotypic expression of complex characters [11].The appropriateness of this concern is exemplified in results reported in this series of reviews. The complexity of maternal environment genotype interactions is illustrated by the results of Myers who showed that WKY mothers emitted maternal behavior characteristic of SHR's if they were presented with a litter of F_1 hybrid pups. In addition, our own studies show that the combination of SHR mothers with hybrid pups results in weanlings less able to withstand the adverse effects of a high salt diet compared to SHR's raised by their own mothers. Henderson's emphasis on appropriate sampling of genotypes and environments is especially apposite to the present research, if we are able to gain an appreciation of how general the effects of early environment are, or how pervasive are the kinds of maternal environment/genotype interactions reported in these reviews. Carlier, Roubertoux and associates have also made important contributons to this topic by developing innovative experimental designs which permit the investigator to distinguish between the role of the pup and the role of the mother in influencing a variety of physiological and behavioral characters in inbred mice [7]. Sampling considerations, similar to those discussed by Henderson, are also pertinent to generalizations about the relative importance of genes and environment in hypertension which are arrived at on the basis of the present work. Crosses between selected strains usually provide inflated estimates of the role of genes in the expression of a character, relative to the importance of the relevant alleles in an unselected population. In addition, since environmental variation is usually held to a minimum when conducting genetic crosses with such strains, the potential contribution of environmental variations is usually not fully appreciated. An important point arising from the above is that one must be cautious about generalizing from these models or, making inferences which have species-wide, or, indeed, inter-specific applicability. A useful review of genetic studies conducted with hypertensive models has recently been published by Schlager [22].

This area of research represents an interesting synthesis between behavior genetics and developmental psychobiology. We will not be able to understand the contribution of maternal genotype, or indeed pup genotype, to phenotypic expression of BP in adult life unless we adopt the experimental designs and research strategies of behavior genetics. Reciprocally, we will not understand the contribution of maternal behavior or any other perturbations during development to physiological and behavioral phenotypes in adult life, unless we steep ourselves in the literature and traditions of developmental psychobiology [23]. This will not be an easy task because of the disparate kinds of training and different outlooks produced by such training within each discipline. However, the pioneering work described in these reviews has opened a window onto a fascinating area of research with major implications for human health. How much of the well-established genetic contributon to BP-variation in humans may depend on maternal/fetal or maternal/neonatal interactions? We do not have any idea of the answer to these questions but the results of these animal studies compel us to treat them seriously.

Although most of the present knowledge points toward a post-natal influence on BP-variation in adult life, the role of the pre-natal environment has hardly been explored. In rats, there are major changes in BP late in pregnancy, and these are especially pronounced in hypertensive animals[1]. Elsewhere, Thomas Folk and I have suggested that these alterations in BP reflect the fundamental process of metabolic and nutrient exchange between fetal and maternal circulations[5]. It ist quite conceivable that the much larger alterations in BP which occur in pregnant hypertensive rats could reflect a fundamental difference in the maternal/fetal exchange process in hypertensive animals and could have a long-term influence on the development of cardiovascular control systems. Thus, any consideration of the implications of the present research for humans should not neglect the possible role of the pre-natal environment in influencing BP levels in adult life.

One of the exciting aspects of this research is that it clearly shows the manner in which genes and environment interact to produce hypertension, and that genes, in fact, can have their effect by altering the environment in which an individual develops. Plomin and Bergeman have coined the phrase the "Nature of Nurture" to draw attention to this important type of genetic influence[21]. As Plomin has argued elsewhere, although the discipline of behavior genetics has frequently been condemned because of its emphasis on the genetic contribution to the expression of a character, the methods of this specialty provide the best means of revealing the environmental contributon to phenotypic expression[20]. The experimental designs and approaches used to study the influence of the maternal environment in animal studies has been most thorougly discussed by Anne McClaren[18]. Within behavior genetics, one of these designs, that involving reciprocal crossing of two inbred strains, was pioneered by Broadhurst, albeit in an attempt to show that maternal influences were not important in behavioral differences between the Maudsley strains[6]. However, in recent years, in animal studies, the impact of the maternal environment has been systematically explored by a variety of methods by Carlier, Roubertoux and associates[7]. In these studies, careful attention has been given to understandig the role of both maternal and pup genotype in influencing the mother/pup interaction, and there is much of methodological interest in these studies relevant to research on hypertension. The point is that genes can affect the developmental environment in which an animal is reared in a variety of ways, by altering the pre-natal environment, post-natal maternal care, etc. and that these genetic variations can make an important contribution to phenotypic variation in a variety of characters in adult life. As expressed throughout this review series, the nature of nurture, in the case of the SHR and SS/Jr rat models of hypertension may be that genes fixed within these strains may exert part of their effects on BP in adult life by changing the maternal/neonatal interaction during the pre-weaning period!

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