Maternal family history of hypertension attenuates neonatal pain response

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A B S T R A C T

Reduced sensitivity to naturally occurring and laboratory pain stimuli has been observed in individuals with hypertension, high-normal blood pressure, and a family history of hypertension. The present study sought to extend these findings by examining the relationship between familial history of hypertension and pain responsivity in neonates. Eighty infants had intramuscular (IM) injections of vitamin K performed in the delivery room within 1 h of birth as per institutional practice. Video recordings of the injection procedure were used by trained observers to code infant pain responses using facial grimacing and cry duration. Prior to the birth of the child, the infants' parents each completed a family blood pressure history survey and these responses were used to identify infants with and without a maternal and paternal family history of hypertension. As compared to infants without a maternal family history of hypertension, infants with a maternal family history of hypertension had significantly shorter crying times, $F(1,74) = 6.96$, $p = .01$, $\eta^2 = .086$, and marginally lower facial grimacing scores, $F(1,74) = 2.68$, $p = .10$, $\eta^2 = .035$, during vitamin K injection. The presence of attenuated responses to the IM injection in neonates with a maternal family history of hypertension provides important and novel evidence that reduced pain responding in individuals at risk for hypertension is not a learned response style, but rather may arise from prenatal or genetic influences.

1. Introduction

Nearly three decades of research has supported a link between blood pressure and pain perception. Specifically, reduced sensitivity to a variety of naturally occurring and laboratory pain stimuli has been observed in individuals with hypertension [16–18,22–24,39–42,47,57], high-normal blood pressure [2,9,17,27,29,33,46], and a family history of hypertension. [1,5,10,11,13,30,33]. Although evidence of hypertensive hypoalgesia has also been obtained in laboratory animal studies [28,35–37,48,50,52,56], an important limitation inherent in human studies is the possibility that the hypertensive hypoalgesic effect reflects a decreased willingness to report pain rather than a higher pain threshold. This notion is supported in part by longstanding psychosomatic theories and some empirical evidence associating hypertension and risk for hypertension with affective blunting or inhibition of verbal and motoric expression of negative emotional experience [8,25,34,55]. While it is difficult to refute this hypothesis due to the inherently subjective nature of the pain experience, studies that have compared nociceptive flexion reflex (NFR) thresholds in offspring of hypertensive and normotensive parents provide an important insight. The NFR is a polysynaptic spinal reflex that provides an objective index of individual differences in nociceptive threshold. In the NFR paradigm, electrical stimulation is applied to the surface of the foot to determine the minimum intensity required to activate small diameter (i.e., A-delta) nociceptive fibers and a corresponding withdrawal response in the hamstring muscles of the upper leg. Comparison of NFR thresholds in healthy young adults with and without a parental history of hypertension reveals higher thresholds in offspring of hypertensive parents [14,15,33], suggesting that greater nociceptive input is required to elicit pain in those at increased risk for hypertension.

The present study provides an additional, unique test of the relationship between risk for hypertension and pain perception in neonates with and without a family history of hypertension. As part of two separate investigations [45,49], parental family history of hypertension was obtained before labor and delivery. Neonatal pain responses were assessed during routine IM injection of vitamin K (to help prevent hemorrhagic disease of the newborn).

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Because vitamin K injection is administered within an hour of birth, the present approach provides a rare opportunity to examine pain responses that are unlikely to be influenced by conditioning or social learning. Based on the prior evidence of attenuated pain responsivity in young adults at risk for hypertension, we hypothesized that infants with a family history of hypertension would exhibit a decreased pain responsivity as compared to infants without a family history of hypertension.

2. Methods

2.1. Participants

Data for this study were obtained from a subset of patients recruited as part of two double-blind, placebo-controlled randomized trials (RCTs) conducted in the Labor and Delivery Unit of Mount Sinai Hospital, Toronto, Canada [45,49]. In these studies, neonatal pain responses were assessed during routine IM injection of vitamin K. These studies were designed to test different interventions [sucrose 24% solution [49] and amethocaine 4% gel [45]] to reduce newborn pain responses; however, when compared to the placebo control, the treatments did not significantly influence infant pain response to vitamin K injection. That is, neither drug proved more effective than a placebo control condition in reducing infant pain responses to vitamin K injection. Infants in these RCTs were included in the present study if both parents completed a survey describing their family history of hypertension.

2.2. Procedures

2.2.1. Family history of hypertension

The fathers and mothers of each infant were asked to complete a personal blood pressure history survey [32] prior to the birth of their child. Each parent completed a separate survey for their own family history. The survey inquired about age, blood pressure history (including typical blood pressure, prior diagnosis of hypertension, and antihypertensive medication prescription), and history of hypertension in first-degree relatives. Although prior studies on the relationship between pain and risk for hypertension have typically compared pain ratings in those with and without a parental history of hypertension (e.g., see France [11]), the present study used an approach to assess family history effects that was novel in two important respects. First, because of the very low incidence of hypertension in these young parents, family history of hypertension was determined on the basis of the infants' grandparents' blood pressure histories. Second, based on the evidence of specific maternal prenatal and genetic influences on risk for hypertension [7,26,54], we chose to consider the potential independent contribution of both maternal and paternal family histories.

Specifically, infants were defined as having (1) a maternal family history of hypertension if at least one of the mother's parents was reported to have had a prior diagnosis of hypertension, (2) a paternal family history of hypertension if at least one of the father's parents was reported to have had a prior diagnosis of hypertension, or (3) no family history of hypertension if neither the maternal nor the paternal grandparents were reported to have had a history of hypertension. It should be noted that paternal and maternal grandparent blood pressure histories were based on the surveys completed by the infants' father and mother, respectively, and were not independently confirmed.

2.2.2. Vitamin K injection

The IM injection of vitamin K was performed in the delivery room within 1 h of birth as per institutional practice. The neonates were positioned supine on a resuscitation table. A digital video camera (Sony DCR-TRV530 or DCR-TRV25, Sony Electronics Inc, USA) was focused on the infant's face to record reactions to the injection. Except for exposure of the leg that was used for the injection procedure, the infants were swaddled to prevent hand movements obstructing the view of the face. A certified nurse or a physician injected the infant with 0.5 ml of vitamin K (Sabex Inc, Canada) using a 1 ml tuberculin syringe with a 25-gauge needle (5/8" (16-mm) in depth) [19]. The skin of the thigh was stretched flat between the finger and the thumb and the needle was pushed down at 90° angle through the skin. The injection technique was based on the guidelines recommended by the World Health Organization [53]. The injection procedure included four phases: (1) baseline, (2) cleaning the thigh, (3) injection, which included inserting the needle into the thigh, aspirating to check whether a vessel had been punctured and delivering the volume of injection, and (4) recovery.

2.2.3. Infant pain assessment

Neonatal facial grimacing and cry duration measures were scored from the videotaped recordings of the vitamin K injection. Percentage of facial grimacing was calculated on the basis of presence or absence of the three facial actions (brow bulge, eyes squeeze and deepening of the naso-labial furrow) during 2-s intervals for the first 20 s (or less if the phase lasted <20 s) of each procedure phase from the videotapes. The same coding procedure was used for all phases. These three facial actions were chosen for the study as they have been observed in 99% of neonates within 6 s of an invasive procedure (heel lance), and are believed to be the most sensitive indicators of infant pain [20]. The facial action data were collapsed for each facial action into the percentage of time the infant expressed the action (i.e., 0–100%), and an overall score was computed by summing the percentage scores for the three facial actions and then dividing by three. The percentage of time that the infant cried during each phase was defined as the presence of audible vocalizations associated with facial grimacing. [21,58]. The pain measures were scored by a single trained research assistant (a different one for each RCT), who was not present during the videotaping, blind to the study hypotheses, and unaware of the infant's family history of hypertension. Data on the inter-rater reliability were available for facial grimacing (ICC (±95% CI): 0.83 (0.76–0.93)) but not for cry duration.

This study was approved by the research ethics boards at Mount Sinai Hospital and the Hospital For Sick Children and the Human Participants Review Committee at York University. Parents of potentially eligible neonates were identified and approached for written consent and information concerning their family blood pressure histories prior to their child's birth.

2.3. Statistical analysis

To examine the effect of family history of hypertension on infant pain responses, a 2 (maternal family history of hypertension) by 2 (paternal family history of hypertension) MANOVA was conducted using difference scores (injection phase – baseline phase) for both grimacing and crying time as the dependent variables. Demographic and clinical variables were analyzed by one-way ANOVA.

3. Results

Eighty parent couples returned completed family history of hypertension forms that could be scored for the presence or absence of hypertension in the infants' parents and grandparents.

There were no significant differences between the infants with and without a maternal or paternal family history of hypertension

Table 1
Mean (95% CI) for descriptive characteristics of infants with and without a maternal family history of hypertension.

	Positive maternal family history	Negative maternal family history	p	η^2
Birth weight (Kg)	3.54 (3.39–3.68)	3.434 (3.30–3.60)	.29	.014
Gestational age (weeks)	39.24 (38.88–39.59)	39.26 (38.94–39.58)	.92	.000
Mother's age (years)	34.5 (32.9–36.0)	32.9 (31.5–34.2)	.11	.035
Father's age (years)	36.9 (35.3–38.5)	35.2 (33.4–37.0)	.16	.026

in terms of birth weight, gestational age, maternal age or paternal age. Descriptive characteristics of infants as a function of maternal family history of hypertension are provided in Table 1. There were 42 infants with and 38 without a paternal family history of hypertension, and 39 infants with and 41 without a maternal family history of hypertension.

Results of the MANOVA revealed a significant main effect of maternal family history of hypertension, $F(2,73) = 3.49$, $p < 0.05$, $\eta^2 = .087$, but no significant effect of paternal family history of hypertension, $F(2,73) = 0.91$, $p = 0.40$, $\eta^2 = .024$. The interaction effect was also non-significant. As can be seen in Table 2, follow-up ANOVAs of the maternal family history effect revealed significantly shorter crying times, $F(1,74) = 6.96$, $p = .01$, $\eta^2 = .086$, and marginally lower facial grimacing scores, $F(1,74) = 2.68$, $p = .10$, $\eta^2 = .035$, for offspring of mothers with a family history of hypertension versus those without a family history of hypertension. The maternal history effect remained significant after controlling for the treatment group to which the infants had been assigned in the original RCTs (i.e., sucrose [49] or amethocaine [45] versus placebo) and did not differ as a function of infant sex.

4. Discussion

The present study demonstrates a relationship between family history of hypertension and decreased pain responsivity to an IM injection in the newborn infants. Specifically, compared to infants without a maternal family history of hypertension, neonates with a maternal family history showed significantly smaller increases in crying time and marginally smaller increases in facial actions in response to the injection. These results provide novel evidence that risk for hypertension may be associated with decreased pain not as a result of social learning or environmental reinforcement, but rather as a result of undetermined prenatal or genetic influences in healthy infants with a maternal family history of hypertension.

Although this is the first study to examine hypoalgesia in infants at increased genetic risk for hypertension, similar results had previously been noted in animals. For example, spontaneously hypertensive rats (SHRs), which have been selectively bred to develop hypertension, demonstrate reduced responsiveness to nociceptive stimuli as early as the third week of life [43,48]. Interestingly, exaggerated endogenous opiate activity has been identified as a mediator of hypoalgesia in SHR, since administration of the opiate-receptor antagonist naloxone normalizes nociceptive responding [6,48,52]. Whereas elevated plasma opioid levels have been reported in hypertensive humans [22,31,47], opiate-receptor blockade studies have yielded mixed results. McCubbin and colleagues [30] demonstrated that naltrexone reversed the reduced sensitivity to cold pressor pain in those with high-normal blood pressure, and that this effect was most pronounced in those with high-normal blood pressure and a positive family history of hypertension. In contrast, in other studies opiate-receptor blockade has failed to significantly alter nociceptive responding in individuals with hypertension [38,39], high-normal blood pressure [29,44], or normotensive individuals with a family history of hypertension [12].

Table 2
Mean (95% CI) values for change (% during vitamin K injection minus % during pre-injection baseline) in infant facial grimacing and crying time as a function of maternal and paternal family history of hypertension.

	Positive family history	Negative family history	p	η^2
Facial grimacing				
Maternal	46.4 (33.2–59.6)	61.4 (48.7–74.0)	.10	.035
Paternal	57.4 (45.1–69.8)	50.3 (36.9–63.8)	.44	.008
Crying time				
Maternal	27.3 (15.9–38.7)	48.2 (37.3–59.1)	.01	.086
Paternal	43.1 (32.4–53.7)	32.4 (20.7–44.0)	.18	.024

The demonstration of decreased pain responsivity in infants with a maternal family history of hypertension is perhaps most important in that it provides evidence of an early onset of hypoalgesia; however, this finding is unique and interesting in at least two additional respects. First, whereas prior studies have demonstrated lower pain scores as a function of hypertension or a parental history of hypertension [1,5,10,11,13,30,33], this is the first time that such an effect has been reported as a function of blood pressure histories collected from grandparents. This suggests that the effect of family history of hypertension on hypoalgesic responding may be transmitted from one generation to the next, and that inheritance effects may be best estimated on the basis of a more extensive family history that goes beyond a single generation. Second, this is also the first study to examine hypoalgesic responses independently for maternal and paternal family blood pressure history. Accordingly, consistent with our finding that hypoalgesia was associated exclusively with maternal transmission of risk for hypertension, it is possible that prior findings of reduced pain responsivity in offspring of hypertensives may have been due primarily to maternal family history versus paternal family history. This notion is consistent with the emerging evidence of a maternal influence on the transmission of risk for hypertension [7,26,54]. Specifically, recent genetic studies demonstrate an involvement of mitochondrial DNA mutations in the development of hypertension in some families. Because mitochondrial DNA is inherited exclusively from the mother, these studies suggest a mode of inheritance of risk for hypertension that is based on a maternal transmission pattern. Accordingly, the present findings suggest that additional consideration of maternal inheritance may provide important clues in the ongoing search for potential mechanisms of hypertensive hypoalgesia in humans.

Although the present findings are intriguing, it must be noted that there are limitations to the study and methods. First, this was a pilot study including a subsample of infants, who were recruited as a part of two separate randomized controlled trials. It is, therefore, advisable that the findings be reproduced on a larger sample of infants. A larger sample size may also help address a second limitation, which relates to the fact that we observed significant group differences in infant cry times but only marginal differences in facial grimacing. Significant differences on both variables may be obtained with larger samples; however, the observed effect sizes were small, and this may be related to the challenge inherent in accurately identifying infant risk for hypertension on the basis of familial history reports. Specifically, an important limitation in all studies that use family history as a marker of hypertensive risk is the potential for both false-positive and false-negative group assignments. False positives occur when those identified as at high risk based on family history do not go on to develop the disorder, whereas false negatives occur when those identified as at low risk based on familial history go on to develop hypertension. Because these problems occur at varying and unknown rates, the error variance associated with risk group

assignment is likely inflated. A third and potentially related limitation is that mothers in the present sample were approximately two years younger than the fathers. Although this is a small age difference, this could increase false negatives in the maternal family history (i.e., the maternal grandparents may be younger and, therefore, may be less likely to have developed hypertension) and reduce false positives in the maternal family history as a younger diagnosis of hypertension is associated with a higher risk for the disorder in the next generation [51]. A fourth limitation is that in the present study, parental reports of hypertension in themselves or their family were not confirmed; given that prior studies have only considered a parental history of hypertension, it would be beneficial to conduct more extensive pedigree charts to provide comprehensive assessment of family history of hypertension. Finally, the absence of specific data on inter-rater reliably for cry duration is a limitation, although coders were trained and participated in inter-rater reliability testing prior to the study. Notwithstanding these caveats, from a practical perspective hypoalgesia may serve as a valuable method of identifying those at greatest risk for hypertension among otherwise heterogeneous groups of offspring of hypertensives. Consistent with this notion, Campbell and colleagues [3,4] followed a sample of young males from adolescence until early adulthood and reported that early hypoalgesia was a significant predictor of blood pressure up to eight years later, even after controlling for parental history of hypertension and initial resting blood pressure levels. Although longer follow-up studies are needed to examine the potential unique and interactive relationship between hypoalgesia and family history in the prediction of actual hypertension, hypoalgesia appears to add additional variance to the prediction of future blood pressure, and thus may serve as a behavioral marker of hypertensive risk that could be used to promote early and efficient identification of strong candidates for pharmacological and non-pharmacological prevention efforts.

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