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Spontaneous genetic hypertension in the rat and its relationship to reduced ac cochlear potentials: Implications for preservation of human hearing

(presbycusis/microcirculation/platelets/natriuretic hormone)

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ABSTRACT **We present controlled laboratory studies of the spontaneously hypertensive rat which indicate that hypertension is an important pathophysiological risk factor in age-related hearing loss. Our results are in concert with previous retrospective clinical studies that pointed to this possibility in man. Hypertension as a risk factor for hearing loss is within the bounds of known measures of diagnosis, treatment, and even prevention, with monitoring early in life. Because hypertension is such a major public health problem in the United States, in view of our results it is possible that its treatment and early diagnosis will benefit a significant number of people who would otherwise lose their hearing with advancing age. We compared the round window ac cochlear potential-sensitivity and -intensity functions in 10 female spontaneously hypertensive rats and 10 female normotensive Wistar–Kyoto control rats. The animals were all 12 months old and weighed between 170 and 250 g. The normotensives had higher maximum cochlear potential-intensity values compared with the hypertensives: 1,000 Hz ($P < 0.005$), 5,000 Hz ($P < 0.005$), and 10,000 Hz ($P < 0.01$). One-microvolt isopotential cochlear potentials for the low frequencies of the normotensives showed greater sensitivity than those of the hypertensives: 100 Hz ($P < 0.05$), 200 Hz ($P < 0.10$), 290 Hz ($P < 0.05$), 500 Hz ($P < 0.005$), 700 Hz ($P < 0.12$), 1,000 Hz ($P < 0.025$), and 2,000 Hz ($P < 0.10$). Blood pressure of the hypertensive group was significantly greater than that of the normotensive rats ($P < 0.001$). The hearts and aortas of the hypertensive group were hypertrophied. Autonomic imbalance, platelet aggregation, decreased arterioles, and natriuretic hormone were discussed as possible etiologies for the measured sensory hearing loss.**

An important frontier for clinical otologists and scientists in physiological acoustics is the study of the etiology of presbycusis (1). This paper represents a new approach to the problem, and our results could have far-reaching significance for the potential amelioration of progressive loss of hearing with old age. We focused our attention on hypertension, which is a major pathophysiological process associated with aging. We found a striking correlation between hypertension and hearing loss in a controlled laboratory experiment. Thus, we identified a risk factor for hearing loss that is within the bounds of known measures of diagnosis, treatment, and even prevention, with monitoring early in life.

Previous work on presbycusis—although not defining its pathophysiology—has served to document the histopathological nature of inner ear degeneration with age (2, 3). Other important studies have delineated the contributions of noise and ototoxic drugs to loss of hearing with age (4). Even earlier laboratory experiments have explained in detail the principles behind the otologist's operations for conductive deafness in people (5).

Our experiments were motivated in part by conflicting retrospective clinical studies in the literature. Some reports have found a positive correlation between hearing loss and hypertension in people (6–8). Others have not found this relationship (9, 10).

Further impetus for our effort was the fact that hypertension itself is such an important problem in the United States. The 1962 U.S. National Health Survey estimated that 26 million Americans (20% of the adult population) had hypertension, and more recent studies indicate that even a higher percentage of the population suffers from this disorder (11). Such a broad-based problem as hypertension, when tied to hearing loss, offers the hope of hearing conservation for many people.

For our animal model we used the spontaneously hypertensive rat (SHR), which was developed by selective inbreeding of the Wistar–Kyoto rat. Normotensive rats of the Wistar–Kyoto strain (WKY) were used as age-matched controls (12).

To measure the hearing capability of our animals, we recorded the round window ac cochlear potentials (13). Extensive baseline studies of the cochlear potentials in the rat have been carried out by Crowley and Hepp-Reymond and colleagues (14, 15). We were especially drawn to use the method of recording ac cochlear potentials because Wever *et al.* (16) have shown that the cochlear potential maximum-intensity function is highly correlated with the number of viable sensory hair cells in the inner ear. Furthermore, Lawrence (17) has discovered a direct metabolic dependence of the sensory hair cells on a discrete microcirculatory bed in the inner ear: the vas spirale. Such a system potentially could be influenced by changes in systemic blood pressure (18).

Using another animal model for human vascular disease, the white carneau pigeon (19, 20), we also have made a preliminary report of a positive correlation between cochlear potentials and blood pressure (21). One of the most important aspects of this study was the finding of a loss of cochlear potentials with the occurrence of hypertension, followed by a recovery of potentials with a subsequent drop in blood pressure. This biphasic response pattern took place over many months of the animals' lives, giving the encouraging and very significant finding that sensory hair cells can suffer a temporary metabolic suppression with hypertension. This, of course, adds hope not only for prevention of hearing loss with prevention of hypertension but also for correction of hearing loss with treatment of hypertension. The results of this study will be discussed in a future full report.

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Abbreviations: SHR, spontaneously hypertensive rat; WKY, normotensive Wistar–Kyoto rat.

MATERIALS AND METHODS

Subjects. Ten female SHRs and 10 female WKYs obtained from the Charles River Breeding Laboratories were used in the study. The animals were all 12 months old and weighed between 170 and 250 g. Because of the possibility of artifactual round window fistula, one WKY was eliminated from the cochlear potential-data analysis.

Recording of Blood Pressure. Systolic blood pressure of the rats was measured by the tail-cuff technique (22). Each animal was measured at least three times at four recording sessions over a 2-wk period. An average of the four readings was used for statistical purposes.

Recording of Cochlear Potential. The surgery, anesthesia, sound stimulation, and cochlear potential-recording procedures that we used have been described (23). Briefly, a surgical exposure of the round window was made through the mastoid bone, and a silver ball electrode was placed on the round window membrane. The ac cochlear potentials were measured on a 1900-A General Radio Corporation wave analyzer. Both ears of each animal were measured, and the best ear of each animal was used for statistical calculations.

Autopsy. After electrophysiological measurements were completed, the animals were sacrificed with an overdose of anesthetic, and fresh wet weights were made of the right and left kidneys, liver, heart, and aorta.

Statistical Analysis. Student's *t* tests were performed on all of the measurements of cochlear potential sensitivity and intensity and organ weights between the SHR and WKY groups. The degrees of freedom were changed from comparison to comparison to help to compensate for the bias induced by multiple comparisons. Spearman rank-order correlations were performed on the intensity measurements for the SHR group.

RESULTS

The systolic blood pressures for the WKY group had a mean of 113 mm of mercury (SEM = 1.63). The systolic blood pressure for the SHR group had a mean of 175 mm of mercury (SEM = 4.60). The *t* ratio was −12.67 with 11.23 degrees of freedom, and the two groups were significantly different ($P < 0.001$).

The body weights for the SHR and WKY groups were not significantly different. When the organ weights of the animals were adjusted by dividing them by the body weight, the heart weights of the SHRs were significantly greater [t (13.25) = −7.17, $P < 0.001$] than those of the WKYs, and the aorta wet weights of the SHRs were greater [t (17.71) = −2.31, $P < 0.025$] than those of the WKYs. The left kidney weights for the SHRs were greater than those of the WKYs [t (12.34) = −1.49, $P < 0.10$], but there was no difference between the weights of SHR and WKY right kidneys. The liver weights of the SHRs were greater than those of the WKYs [t (16.48) = −1.52, $P < 0.10$].

There was good agreement (Fig. 1) between our control WKY cochlear potential-sensitivity data and that previously reported in the literature by Crowley and his colleagues (14). Only 5-, 7-, and 10-kHz means of the previously published sensitivity function were noticeably different from our values. We have not compared the variance of the two groups to determine if these differences in means are significant. Whereas Crowley measured sensitivity up to 70 kHz, we only measured up to 40 kHz. When our cochlear potential-sensitivity data for the SHR and WKY groups were compared, only the low-frequency values for the SHR group were less sensitive than the WKY values: 100 Hz [t (12.76) = −2.03, $P < 0.05$]; 200 Hz [t (15.02) = −1.34, $P < 0.10$]; 290 Hz [t (14.07) = −2.05, $P < 0.05$]; 500 Hz [t (14.60) = −3.71, $P < 0.005$]; 700 Hz [t (17.02) = −1.13, $P < 0.12$]; 1,000 Hz [t (16.36) = −2.13, $P < 0.025$]; and 2,000 Hz [t (12.20) = −1.36, $P < 0.10$]. The mean cochlear potential-sensitivity functions for the SHRs and WKYs are compared in Fig. 2. The mean (±SD) sensitivity values for the WKYs and SHRs are shown in Figs. 3 and 4, respectively.

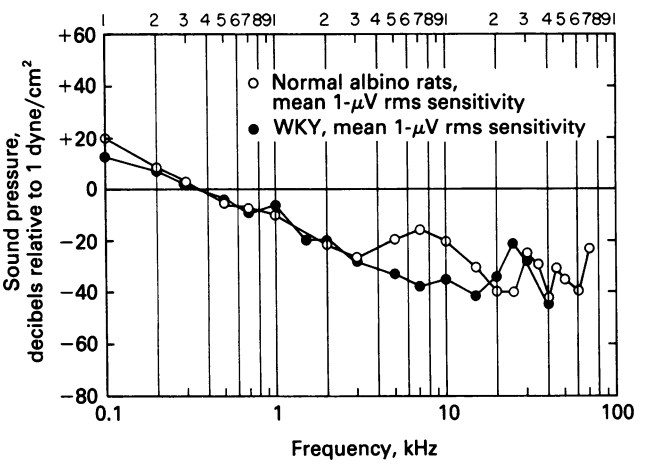

FIG. 1. One-microvolt root-mean-square (rms) isopotential ac cochlear potential-sensitivity measurements from control WKYs of the present study compared with those obtained by Crowley *et al.* (14) on normotensive albino rats.

Sample cochlear potential-intensity functions for a WKY and an SHR are compared in Fig. 5 *a–c*. When the maximum responses for cochlear potential-intensity functions were compared, the WKY group had significantly higher potentials than the SHR group: 1,000 Hz [t (16.90) = 3.83, $P < 0.005$]; 5,000 Hz [t (15.25) = 3.62, $P < 0.005$]; 10,000 Hz [t (16.29) = 2.78, $P < 0.01$]. The data for the intensity maximum-response comparison are depicted in Fig. 6.

When the SHR data were examined alone, the only rank-order correlation between cochlear potentials and systolic blood pressure was a positive correlation, +0.732 ($P < 0.02$), for the 1,000-Hz maximum-intensity data. Also, within the SHR group, there was a slight positive correlation between aorta weight and the 1,000-Hz maximum, +0.543 ($P < 0.10$); a negative correlation between the 5,000-Hz maximum and left kidney weight, −0.662 ($P < 0.05$); and a negative correlation between the 10,000-Hz maximum and left kidney weight, −0.549 ($P < 0.10$).

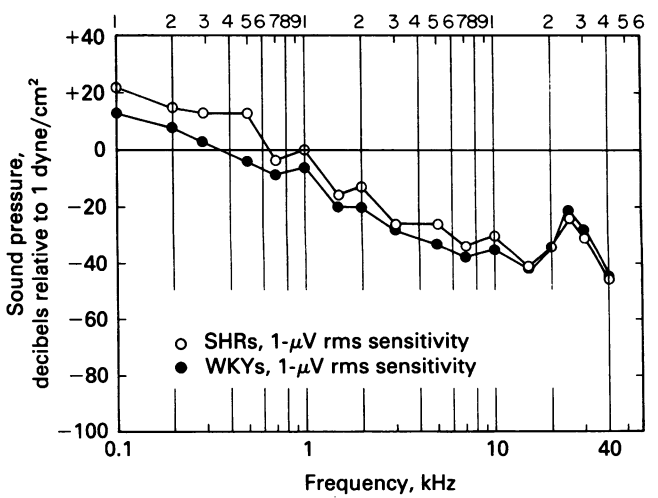

FIG. 2. Mean sensitivity measurements for the WKYs and SHRs. Curves are 1-μV rms ac cochlear potential isopotential functions.

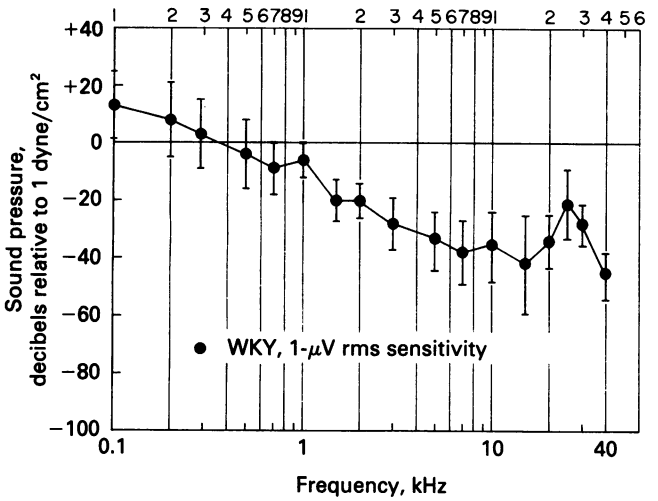

FIG. 3. Mean ± SD sensitivity measurements for the WKYs. Curve is a 1-μV rms isopotential ac cochlear potential function.

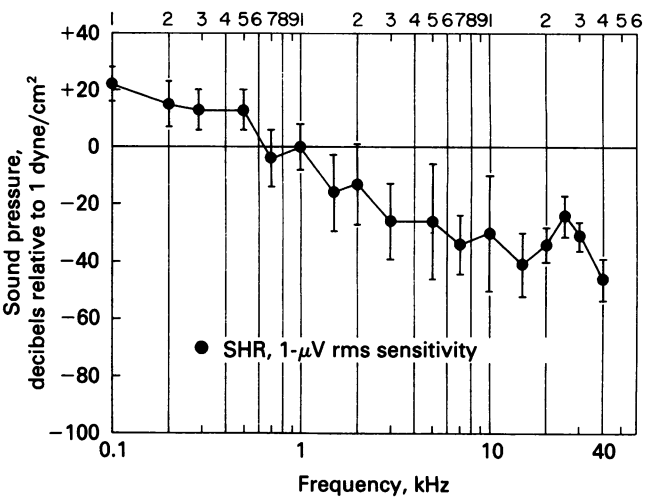

FIG. 4. Mean ± SD sensitivity measurements for the SHRs. Curve is a 1-μV rms isopotential ac cochlear potential function.

DISCUSSION

Reduced Sensory Cell Function. In view of the fact that ac cochlear potential maximum responses are highly correlated with the number of viable sensory hair cells in the inner ear (16), it is reasonable to assume that the SHR subjects suffered from suppression of hair cell function as indicated by their significantly reduced intensity maximums. The relatively minor simultaneous reduction in the SHR of 1-μV isopotential cochlear potential sensitivity may be related to the finding that sensitivity data are not related to the number of inner ear sensory cells (16).

Hypertension and Noise. Our finding of reduced cochlear potential function in the SHR confounds Borg's conclusion that the SHR is more susceptible to noise damage of hearing than the WKY (24). It is possible that the results of Borg are correct, but unfortunately his study did not control or test for a naturally occurring hearing loss apart from one associated with noise exposure in the SHR.

Borg also maintains that industrial noise does not affect blood pressure in the rat (24). However, Peterson and his colleagues have found that industrial noise does raise blood pressure in the rhesus monkey (25). In the light of our finding of hearing loss associated with hypertension, Peterson's observation brings out the interesting speculation that industrial noise hearing loss may be aggravated by noise-induced hypertension as well as by direct stimulation to the inner ear by noise.

Body-Organ Hypertropy. Increased heart weight in the SHR group is in keeping with Okamoto's observation of the same thing (26). He attributed the hypertrophy to increased afterload on the heart. Our reported increase in SHR aorta wet weight is in agreement with Wolinsky (27), and kidney weight changes have been noted (26).

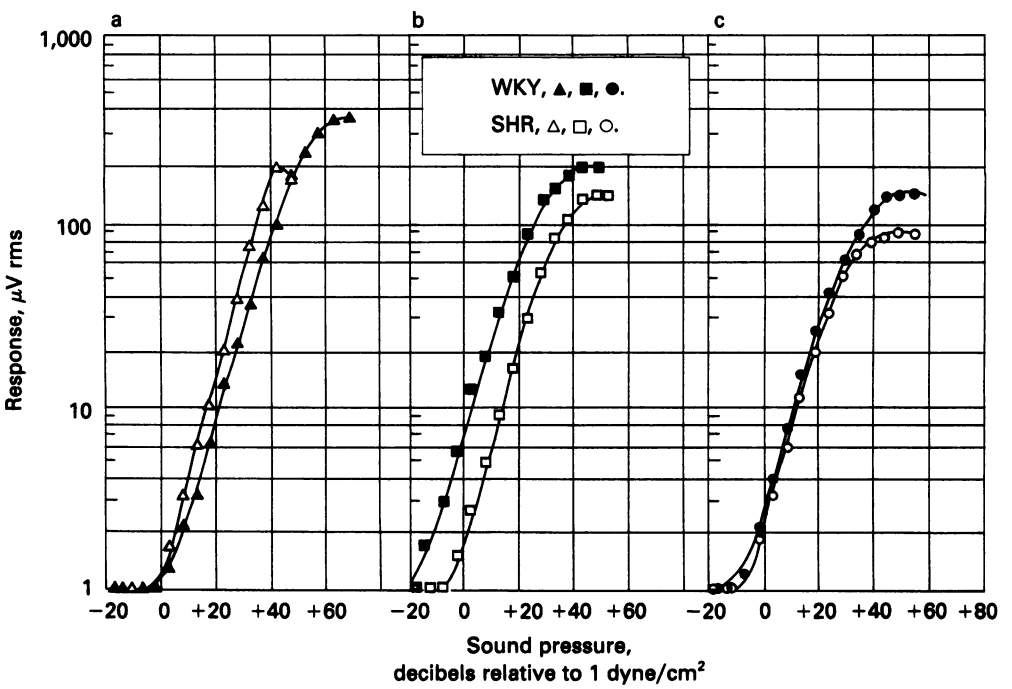

FIG. 5. Typical ac cochlear potential-intensity curves at 1,000 Hz (*a*), 5,000 Hz (*b*), and 10,000 Hz (*c*) for a SHR compared to a WKY.

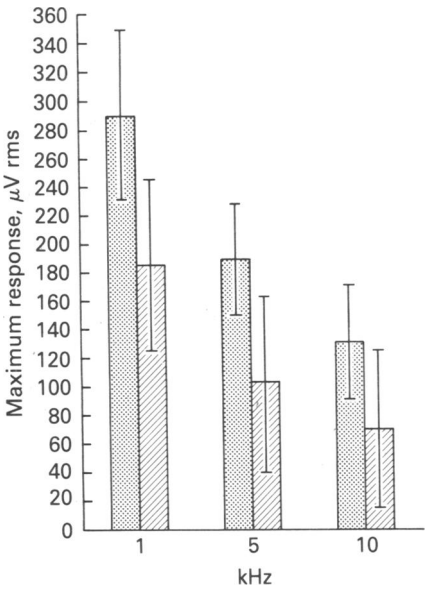

FIG. 6. Mean ± SD maximum ac cochlear potential responses for the WKY (▨) and SHR (▨) at 1,000 Hz ($P < 0.005$), 5,000 Hz ($P < 0.005$), and 10,000 Hz ($P < 0.01$).

The Possibility of an Adaptive System. In his clinical review of hypertension and hearing loss, Furstenburg noted that the degree of duration of hypertension in people did not correlate directly with the amount of hearing loss, even though hearing loss in general was associated with hypertension. Furstenburg found that people with newly acquired hypertension had more severe hearing losses than those with even higher blood pressure that had persisted longer (6). A slight but similar trend was noted in our SHR subjects. These data lead us to speculate that there may be an adaptive process whereby the inner ear can effect some spontaneous recovery from hypertension-induced hearing loss. Thus, a further developmental hearing study of the SHR is warranted to see if there might be some recovery of function in the animal at an age past the one we studied.

Possible Mechanisms. From our controlled laboratory experiment and human retrospective clinical studies (6–8), it now seems apparent that there is a correlation between hypertension and hearing loss. But, it has not yet been established that there is a causal relationship between these two entities. The association is most likely a complex one. Different forms of hypertension may have different etiologies. Furthermore, it is not clear what facets of the hypertension syndrome, if any, may be directly responsible for hearing loss. Increase in pure hydrostatic pressure could itself affect the inner ear microcirculation function as explained by Lawrence (18); but there are also several pathophysiological parameters related to hypertension that may potentially depress the inner ear's performance.

An important speculation discussed in the literature is that dysfunction of the sympathetic nervous system may contribute to the hypertension of the SHR (28, 29). An imbalance of the autonomic nervous system in hypertension could also conceivably affect inner ear function. Although it seems clear from the literature that the autonomic nervous system innervates the inner ear (30, 31), and there are good studies of adrenergic and cholinergic activity in the inner ear (32–34), other papers are in complete disagreement about the influence of the autonomic nervous system on hearing (35, 36). More research is needed to define the role of the autonomic nervous system in hypertension-related hearing loss.

Another pathological finding in the SHR is platelet dysfunction, and this problem could be related to deafness. Hazama *et al.* have found platelet adhesion to the injured endothelial surface of cerebral arteries in the SHR (37). Such platelets could potentially break away from cerebral vessel walls and flow downstream to block the inner ear vasculature. Platelet aggregates already have been found blocking the microcirculation of the kidneys of SHR (38). In our observations of cochlear potential loss with the occurrence of hypertension in the white carneau pigeon, there was a concurrent decrease in systemic platelet (thrombocyte) count and fibrinogen level, indicating an intravascular coagulation process. These parameters returned to baseline levels with a subsequent drop of blood pressure and return of cochlear potential function (21).

Hutchins, who originally interested us in the SHR, and his associate (39) have observed in the 6-wk-old prehypertensive SHR a decrease in the number of small arterioles in the skeletal muscle of the SHR when compared to the WKY. This finding was postulated to play a role in the increase in peripheral resistance seen during later stages of hypertension. In the light of Hutchins' work, we feel that a decrease in inner ear arterioles could help to explain a metabolic reduction of hair cell function. It is encouraging to note that propranolol treatment during the development of the SHR can prevent the decrease of arterioles (40).

Another exciting hypothesis is that a natriuretic hormone that has been isolated and identified (V. M. Buckalew and K. A. Gruber, personal communication) may be one of the direct causes of hypertension-related hearing loss; the natriuretic hormone was found in the blood of hypertensive people and animals, and it may be the cause of many forms of hypertension. According to the tenets of our hypothesis, natriuretic hormone may directly cause sensory neural hearing loss by inhibiting the sodium/potassium pump of the stria vascularis of the inner ear. Additionally or alternatively, natriuretic hormone may cause hypoxia of the stria vascularis or the sensory hair cells, or both, by increasing the vascular reactivity of the arterioles supplying the inner ear. Indeed, a humoral sensitizing factor for norepinephrine in the SHR has recently been discovered (41), and preliminary results in our laboratory indicate that natriuretic hormone samples (prepared in Buckalew's laboratory) can suppress the ac cochlear potentials in guinea pigs. A full report of this work will appear in a future publication.

If natriuretic hormone is involved in the etiology of deafness as well as hypertension, it could open new approaches for identifying those people who are likely to get hypertension and hearing loss—for example, by looking for evidence of increasing levels of the hormone in the plasma of the blood. It could also lead to the development of new therapeutic agents that might reverse hypertension and hearing dysfunction by counteracting the effects of natriuretic hormone. This concept already was proposed for the treatment of hypertension alone by Marx (42).

CONCLUSION

The results reported in this paper go beyond the histopathological description of presbycusis. We have identified hypertension as a pathophysiological concomitant of aging that seems to be an important risk factor for deafness in animals and people. This risk factor for hearing loss is within the bounds of known measures of diagnosis, treatment, and even prevention, with monitoring early in life. Because hypertension is such a major public health problem in the United States, it is possible that its treatment and early diagnosis will benefit a significant number of people who would otherwise lose their hearing with advancing age.

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