3) Inhibition of the pathogenesis of spontaneous hypertension in SHR by
gonadectomy: Difference from adrenal regeneration hypertension. Masanao Hirai,
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Summary
Male spontaneously hypertensive rat (SHR) originated from Kyoto-Wistar (WKY)
were divided into 4 groups; intact, castration (cast) performed at 4 weeks old
(W) and adrenal enucleation (enucl) at 10 W, cast at 4 W and enucl at 22 W, and
enucl at 10 W and cast at 22 W. This would indicate 1) enucl-adrenal in the
presence or absence of gonad increases significantly blood pressure (BP) in both
SHR and WKY, 2) gonadectomy significantly retards BP in both enucl-adrenal
bearing and intact SHR, 3) gonadectomy did not alter the BP in WKY. These
indicates that gonadal hormone(s) play of important role in the etiology of
essential hypertension.

Introduction
It is well known that women before menopause have a lower incidence of
atherosclerotic vascular disease than men of the same age, whereas after meno-
pause, the incidence begins to approach that for men. Estrogen has been shown to
inhibit the development of experimentally induced atherosclerosis in the chick
(1). However, the mechanism by which estrogen protects is not known. Virtually
all women who take estrogen-containing oral contraceptives demonstrate some rise
in blood pressure (2). There are many reports confirming this response but
despite extensive work, the reasons for the blood pressure rise are by no means
fully understood. The administration of testosterone to castrated male rats
resulted in a significantly higher systolic blood pressure than that found in
castrated males (3). Genetically programed spontaneous hypertension of spontane-
ously hypertensive rats (SHR) is mediated by abnormal activity of the hypo-
thalamo-pituitary-adrenal-gonadal axis. SHR are normotensive at birth but as
they mature, their blood pressure begins to rise and increase with age. In
contrast to Okamoto & Aoki (4), we found, as did Iams & Wexler (5, 6) that early
gonadectomy retards the pathogenesis of hypertension in SHR. More recently, we
found that gonadectomy inhibits the usual increase in blood pressure during the
late maturation of SHR suggesting that gonadal hormones may be important in the
maintenance of elevated blood pressure in these genetically hypertensive animals
(7).

Iams et al. (8) found that circulating levels of aldosterone and cortico-
sterone are slightly higher in the SHR than in other strains of rat under both
quiescent and stressful conditions (8, 9). The age of the rat may be of impor-
tance in the relationship between steroidogenesis and hypertension (10). At 14
weeks old, male SHR have significantly lower-adrenal corticosterone levels than
that of WKY and female SHR manifested significantly higher 18-OH-DOC levels than
that of WKY. 11β-Hydroxylation was decreased in male and 18-hydroxylation was
facilitated in female which are significantly appeared in 14 weeks old SHR
suggesting both accumulation of DOC in male and increasing of 18-OH-DOC in female
are involved hypertensinogenic situation, however a similar pattern could not be
appear in finding of 29 weeks old SHR (11). Komanicky (12) mentioned that the
possibility of the secretion of an unknown steroid(s).

It is our contention that the studies of adrenal steroidogenesis in SHR have
produced somewhat paradoxical results. The present work extends our earlier
study on the gonadectomy-reduced spontaneous hypertension and elucidates the
sites whereby gonadectomy exert its inhibitory effects upon spontaneous hyper-
tension and further, to determine the difference between SHR-hypertension
and hypertension obtained from adrenal original, especially regenerating adrenal
by the enucleation.

Materials and Methods
Animals: The SHR used in this experiment were raised in our SHR Breeding
Colony by brother-sister mating of original stock provided by the SHR Association (Kyoto, Japan) through the courtesy of Dr. K. Okamoto. Control animals (WKY) were also derived from the original colony.

Measurement of blood pressure: Systolic blood pressure (BP) was measured weekly by the tail cuff photoelectric method and heart rate by an electronic procedure in conscious rats using a Natsume Blood Pressure instrument Model KN-209 equipped with a digital panel for heart rate and BP.

Comparison of the effects of adrenal enucleation and of orchiectomy in etiology of hypertension in the SHR: Previously, we have reported that the gonadal hormones are involved in the pathogenesis of SHR-hypertension using gonadectomized male and female SHR. In this experiment, therefore, at an age of 4 weeks male SHR were randomly divided in 4 groups; rats in the first group served as controls. Testes and epididymis were removed (castration) at 4 weeks old and adrenal enucleation (incised gland was compressed gently, causing evulsion of the entire contents including cortical and medullary tissue) was made at 10 weeks old as group 2. Castration performed at 4 weeks old and enucleation at 22 weeks old as group 3. Enucleation at 10 weeks old and castration at 22 weeks old as group 4. All rats were given usual water as drinking even though in the adrenal enucleated rats. Measurements of BP were repeated every week for the experimental period from 4 to 38 weeks old.

Results

A). Intact SHR and WKY: In group 1, SHR manifest progressively increasing BP shortly after weaning, and by 8-10 weeks old, stable higher BP (180±20 mmHg) is established and maintained. BP increase slowly again up to 30 weeks.

B). Changes in BP following castration at 4 weeks old in male SHR: Significant decrease of BP appeared 4 weeks following the operation as compared to control group and these lower levels were keeping up to 22 weeks old. At which time, BP were approximately 190 mmHg in intact SHR and 168 mmHg in castrated SHR.

C). Changes in BP following adrenal enucleation at 10 weeks old in male SHR: These rats showed significantly high BP at the beginning of the 3rd week after the operation as compared to control. The rising BP reached to a levels of 236 mmHg at the age of 22 weeks. The maximal difference of BP between intact and enucleated SHR was approximately 49 mmHg.

D). Changes in BP of male SHR received castration at 4 weeks old and adrenal enucleation at 10 weeks old: The castrated rats had significantly lower BP than the intact rats, but the previously castrated rats showed a definite increase (P<0.01) their BP 1 week after enucleation and the BP values reached a level comparable to that of intact SHR in 2 weeks after the operation.

E). Changes in BP of male SHR received castration at 4 weeks old and adrenal enucleation at 22 weeks old: Previously castrated rats (at 4 weeks old) showed a significant decrease of BP levels (P<0.01) as compared to intact SHR, however the rats manifested a significant increase (P<0.01) in their BP levels 3 weeks after the adrenal enucleation (at 22 weeks old) and the BP values reached a level comparable to that of intact SHR up to 38 weeks old as end-point of estimation.

F). Changes in BP of male SHR received adrenal enucleation at 10 weeks old and castration at 22 weeks old: These observation was made up to 38 weeks old. BP in the course of following adrenal enucleation was severely elevated to 236 mmHg at 22 weeks old, but the BP began to decrease immediately following the castration and a significant decrease was found 3 weeks after the operation and the BP values reached a level comparable to that of intact SHR.

Discussion

The present investigation represented that, although the mechanism for the reduction of BP and the site of action remain speculative, it is clear that gonadal hormones contribute to the genesis of spontaneous hypertension and to the maintenance of established hypertension in SHR. On the other hand, it has been well established that induction of adrenal regeneration by the enucleation
induced hypertension in virgin and breeder, spontaneous hypertension (SHR), and Sprague Dawley rats (13). In this experiments with previous reports (7, 10), we showed that BP in previously normotensive virgin WKY, SHR and in previously castrated SHR became greatly elevated by the enucleation. However, intact SHR caused a severe increase in BP up to 236 mmHg (intact SHR: 190 mmHg) at 22 weeks old, in contrast, 4 weeks old-castrated rats caused a significantly low BP as compared to intact SHR, and this rat manifest a significantly high BP following enucleation at 10 weeks old, but the BP values only reached a level comparable to that of intact SHR at 22 weeks old. Similar pattern was shown that 4 weeks old-castrated SHR was received enucleation at 22 weeks old. In this rat also, a significant increase of BP was manifested by the enucleation and the values reached a level comparable to that of intact SHR. However the provocation of increase in BP appeared significantly faster in enucleation at 10 weeks old than that of in enucleation at 22 weeks old rats. The former was at one week and the latter was at 3 weeks after the enucleation. It may difficult to interpret the difference in sensitivity of orchiectomized SHR to adrenal enucleation induced the increase of BP. It is well known that the activities of a great variety of enzymes are altered as result of gonadectomy (14) and that the absence of androgens in the period of maturation sensitizes animals towards the hypertensive stimuli (15, 16). Thus, it can be noted that younger rats to be more susceptible to the hypertensive effect of regenerated adrenal cortical products than sexually matured ones, as important as an interval between castration and enucleation. By the way, it should be emphasized that the significant retardation of hypertensive BP occurred exactly by orchiectomy on both pre- or post-orchiectomized SHR, and also, that a significant decrease of BP could not occur in WKY, on the contrary, adrenal enucleated hypertension occurred both in SHR and WKY. The results indicated that castration retarded in the development of spontaneous hypertension in SHR. In search of the etiology of hypertension, a considerable interest has been evoked in 19-nor-steroids after the isolation by Gomez-Sanchez (17). It is well known that estrogen production increases during pregnancy and that 19-hydroxylation of androgen is a prerequisite for estrogen formation. It remains to be established if the same factor(s) which increases estrogen production during the development of SHR as shown in 14 and 29 weeks old (10, 11) also stimulates the 19-hydroxy pathway of the ovary, which could lead to increased 19-nor-derivative(s) is elevated before weaning (or in the fetal stage), a sufficient period of exposure to this 19-nor-derivative(s) could result in gonadal origin hypertension in SHR. Since removal of the 19-methyl group enhances the hypertensinogenic property, for example, 19-nor-progesterone (18), 19-nor-androstenedione (19) and 19-nor-DOC (20), it should be of considerable interest to investigate the biological activities of these compound from the gonad in SHR.

References
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