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The objective of this study was to determine if males with a deficient androgen receptor would develop hypertension when crossed with a hypertensive parent. Female King-Holtzman rats ($n=15$), heterozygous for the testicular feminization (Tfm) gene, were crossed with male spontaneously hypertensive rats (SHR), and blood pressure was measured weekly from 5–14 weeks in the F_1 hybrid males. Approximately 50% of the F_1 hybrid males were Tfm males and androgen receptor–deficient, and 50% were normal. Blood pressure in the parent King-Holtzman males, Tfms, and female rats was also followed for the same time period. The F_1 normal male hybrids had a significantly higher ($p<0.05$) systolic blood pressure than the Tfm hybrid males after 12 weeks (195 ± 8 versus 170 ± 8 mm Hg, respectively). Blood pressure in the male and Tfm Holtzman rats was 120 ± 5 mm Hg and 110 ± 6 mm Hg, respectively. Castration lowered blood pressure by 38 mm Hg in the hybrid males and 27 mm Hg in the Tfm hybrids. Female F_1 hybrids also showed a pressure rise above that of female Holtzman controls (155 ± 6 mm Hg versus 110 ± 6 mm Hg, $p<0.01$) but lower than the F_1 males and Tfm hybrids. Ovariectomized females with testosterone implants did not show an elevation in blood pressure. Plasma electrolytes, norepinephrine, and cholesterol were not significantly different between normal and Tfm hybrid males. The results suggest that the presence of an androgen receptor and a testis-derived factor mediate the blood pressure rise in the hybrid males. A Y chromosome effect or sex-influenced locus may be involved since both the normal and Tfm males had significantly higher blood pressures than their female siblings. (*Hypertension* 1991;17:1104–1110)

S ex differences in systolic and diastolic blood pressure by age have been reported in most studies of developed societies. The US Public Health Service National Health Survey,[1] The Tecumseh Study,[2] and similar epidemiological longitudinal studies in Norway,[3] Poland,[4] and Japan[5] have reported that men have higher blood pressure than women at younger ages (second through third decade) with a crossover in women to higher pressures in the fourth to sixth decade. The crossover phenomenon appears to be characteristic of nearly all developed societies and is seen most clearly with systolic pressure. Similar conclusions are reached whether the results are expressed as the mean pressure by age and sex or as prevalence of hypertension. There are only a few blood pressure studies in children, but available data suggest that there are no significant sex differences.[6] These studies and experimental studies suggest that the male sex hormones, specifically testosterone, play a role in the sexual differentiation of hypertension.[7-14]

Recently, our laboratory has shown that the Y chromosome is involved in the development of hypertension in the SHR model.[11] As an extension of this research, we have asked the question whether testosterone and the androgen receptor may influence the development of hypertension, and to test this hypothesis, we developed a hybrid animal model having the potential for genes that could produce hypertension and genes that could produce deficient androgen receptors. The animals that are deficient in androgen receptors are referred to as testicular feminized males (Tfm), and they show the developmental effects of androgen deficiency. The Tfm male is a genotypic XY male, but the phenotype of the adult is female and internally there is an undescended testis that secretes testosterone.

The Tfm trait has been studied in rats, mice, and humans and is believed to be transmitted to offspring via the X chromosome.[15-19] Half of the male offspring of a cross of females heterozygous for the trait with normal breeding males are Tfm and the other half are normal; half of the female offspring are carriers and the other half are noncarriers of the trait.

Methods

The parental SHR strain was obtained from Harlan Sprague Dawley, Indianapolis, Ind., which obtained

the initial breeding stock from the National Institutes of Health (NIH). According to the most current Harlan Sprague Dawley genetic monitoring report, this strain is comparable with most genetically authentic hypertensive strains in the United States that were derived from the NIH colonies (personal communication, Harlan Sprague Dawley, 1988). The parental strain of King-Holtzman Tfm rats was obtained as a generous gift from Dr. Richard Krieg Jr. at the Medical College of Virginia. Their colony, in turn, was derived from a colony at the University of Oklahoma and is often referred to as the Stanley-Grumbach strain (the strain having been named for its developers).

Experiment 1

Females carrying the Tfm gene were bred to spontaneously hypertensive rat (SHR) males. Normal male and female and Tfm male offspring were obtained and their blood pressure was measured from 5 to 14 weeks of age. A typical breeding box (40×50×20 cm) consisted of three females and one male housed in aspen shavings (changed once per week, American Excelsior, Cleveland, Ohio) and provided with water and Purina lab chow ad libitum. Ten such breeding cages were established ($n=30$ females, 10 males). Room temperature (26°–28°C) and humidity (40–50%) were maintained at slightly higher than usual levels to minimize respiratory infections. The 12-hour light/dark cycle (6:00 AM–6:00 PM, light; 6:00 PM–6:00 AM, dark) was kept constant. Litters were weaned and grouped by sex at 3 weeks of age and maintained by sibling group and sex for the duration of the experiments. Both normal male and Tfm-matched siblings were kept in the same cage and ear tagged with metal number clips. The following groups of rats were used ($n=8–12$/group): normal hybrid males, hybrid Tfm, and hybrid females. In addition, blood pressure was measured in the normal females and males of the parent strain: normal King-Holtzman males ($n=12$), Tfm rats ($n=10$), King-Holtzman females ($n=12$), SHR males ($n=10$), and SHR females ($n=12$). Blood pressures were measured weekly between 5 and 14 weeks of age in King-Holtzman hybrid groups and between 5 and 20 weeks in SHR by tail sphygmomanometry (International Biomedical, Inc., Austin, Tex.).[20] Each cage of rats was placed one at a time for 30 minutes in a preheated warming chamber (39°C), and each rat put into a plastic restraint before having five blood pressures taken, which took 2–3 minutes. This technique was performed on conscious animals and, due to the overall chamber warming, the animals were lethargic and vasodilated and did not struggle during the procedure. Weekly pressures and body weights were measured by the same technician without knowledge of experimental group or objective. Trunk blood was collected on termination for analysis of testosterone, norepinephrine, cholesterol, and electrolytes. Plasma testosterone was determined by radioimmunoassay (Radioassays Systems Labora-

tory, Carson, Calif.), catecholamines by high-performance liquid chromatography with electrochemical detection,[21] and electrolytes and cholesterol by an automated colorimetric procedure (Technicon, Southgate Medical Lab, Cleveland, Ohio).

The following organs were removed and weighed on termination: pituitary, adrenal glands, testes, and heart ventricles. Weights were recorded as relative weight per 100 grams body weight.

Experiment 2

The objective of experiment 2 was to determine the effects of prepubertal castration on blood pressure in both the normal hybrid males and the hybrid Tfm animals. At 5 weeks of age, castrations were performed on normal males ($n=10$) and Tfm rats ($n=10$) under sodium brevital anesthesia (50 mg/kg i.p., Eli Lilly and Co., Indianapolis, Ind.) using an abdominal incision. Ethicon suture (5-0) (Ethicon Inc., Somerville, N.J.) was used to close the wounds, and 5,000 units of penicillin G were given intramuscularly. The rats were allowed 1 week of recovery before blood pressures were measured as in experiment 1. Trunk blood was collected at termination for plasma testosterone as in experiment 1.

Experiment 3

The objective of experiment 3 was to determine the effects of ovariectomy and testosterone administration on blood pressure in the hybrid females. Three groups of females (5 weeks of age) were used: controls with intact ovaries ($n=12$), ovariectomized females with testosterone implants ($n=6$), and ovariectomized females with sham implants ($n=6$). Testosterone implants were made from Silastic tubing (Dow Corning, Midland, Mich.) having a packing length of 19 mm (i.d. 0.062 mm, o.d. 0.125 mm). After packing with testosterone proprionate (10 mg) (Steraloids Inc.) the ends were sealed with Silastic medical grade silicone adhesive (Type A, Dow Corning). The implants were cured overnight and soaked in 70% ethanol for 2 hours before implanting them. The sham tube was empty. The tubes were placed in the neck region subcutaneously and were replaced with new implants every 3 weeks under ether anesthesia. The ovariectomy was performed under sodium brevital anesthesia (50 mg/kg i.p.), and Ethicon suture (5-0) was used to close the wound. Rats were given 5,000 units of penicillin G and were allowed to recover for 1 week before blood pressures were taken as in experiment 1. On termination, trunk blood was collected for testosterone measurement as in experiment 1.

Statistical analysis was performed by two-way analysis of variance (ANOVA), Scheffe's test, and Student's *t* tests (one-tailed). The animals were maintained in a humane way according to NIH guidelines.

Results

A female Tfm gene carrier having a slightly gray-colored coat was crossed with a pure white male SHR.
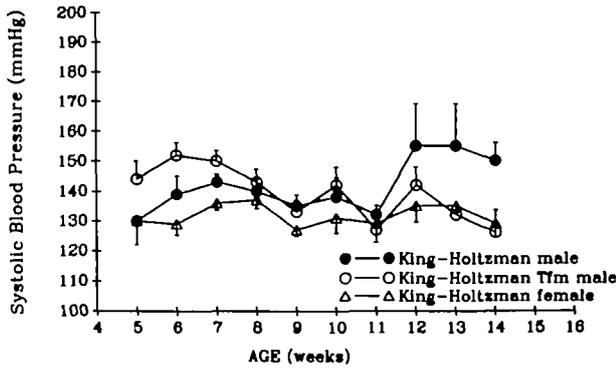
FIGURE 1.   *Line graph showing systolic blood pressure of normotensive King-Holtzman males, King-Holtzman females, and King-Holtzman testicular feminized male (Tfm) rats between 5 and 14 weeks of age (mean±SEM).*

The F_1 offspring (100%) of such a cross had a black dorsal coat.

The blood pressure results for experiment 1 will be presented by first showing the blood pressures of each parental strain and then the pressures of the F_1 hybrid strains.

There were significant differences (two-way ANOVA, group effect: $F=9.5$, $p<0.001$; age effect: $F=2.4$, $p<0.05$; interaction: $F=1.7$, $p<0.05$) in blood pressure over time between the King-Holtzman males, King-Holtzman Tfm animals, and King-Holtzman females (Figure 1). Overall, the pressures of these groups were in the normotensive range, although the normal androgen receptor males showed a slight unexplained significant elevation between 12 and 14 weeks as compared with females and Tfm rats ($p<0.01$, t test). This rise was also seen in male SHR and hybrids between 11 and 14 weeks. Also, the Tfm rats had slightly higher pressures than the females or normal King-Holtzman males at 5 weeks ($p<0.05$, t test). Figure 2 shows the typical marked elevation of blood pressure in SHR males at 14–20 weeks when compared with females (230 versus 160 mm Hg, respectively, $p<0.001$). Blood pressure in the F_1
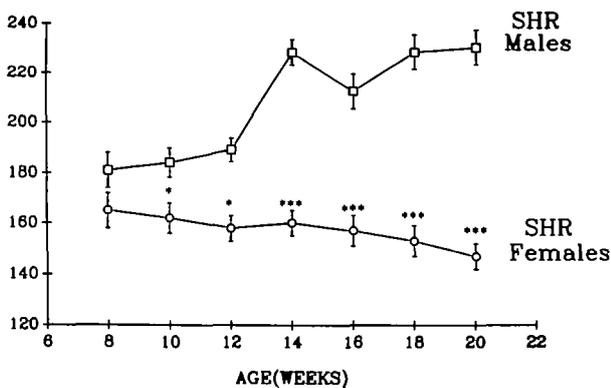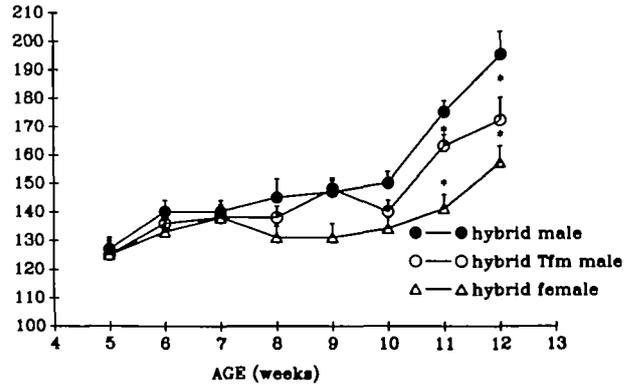

FIGURE 3.   *Line graph showing systolic blood pressure of F_1 hybrids (testicular feminized male [Tfm] carrier female×SHR male). Normal androgen receptor males, Tfm-androgen-deficient males, and females between 5 and 12 weeks of age are compared. *p<0.05, **p<0.01 compared with normal androgen receptor males, t test, mean±SEM).*

hybrid rats is illustrated in Figure 3. The normal males exhibited a rapid rise in blood pressure after 12 weeks into the hypertensive range (195 mm Hg) when compared with the significantly lower pressure of their hybrid Tfm (170 mm Hg; $p<0.05$, t test) and female (155 mm Hg; $p<0.05$, t test) siblings (two-way ANOVA, group effect: $F=21.5$, $p<0.001$; age effect: $F=30.9$, $p<0.001$; interaction: $F=3.8$, $p<0.001$). The female hybrids had significantly lower blood pressure than the normal hybrid males ($p<0.05$, t test) at 11 and 12 weeks, but there were no significant differences compared with hybrid Tfm rats (t test). The effects of castration on blood pressure (experiment 2) are seen in Figure 4. Castration significantly (t tests) lowered blood pressure by 38 mm Hg ($p<0.01$) in the hybrid males and by 27 mm Hg ($p<0.01$) in the Tfm hybrids. The blood pressure difference between the hybrid Tfm and its normal androgen receptor sibling male remained significant after castration. Plasma

FIGURE 2.   *Line graph showing systolic blood pressure of spontaneously hypertensive male and female rats (SHR) between 8 and 20 weeks of age. *p<0.05, ***p<0.001, t tests, mean±SEM.*
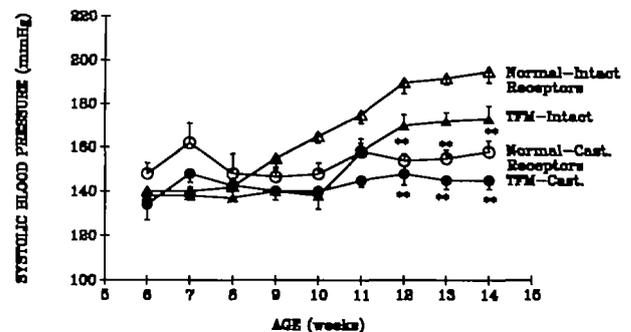

FIGURE 4.   *Line graph showing systolic blood pressure of castrated (Cast.) normal androgen receptor male hybrids and castrated testicular feminized male (Tfm) hybrids (Tfm carrier female×spontaneously hypertensive rat male) as compared with their respective counterpart group with intact testes (mean±SEM). **p<0.01, castrated group compared with respective intact group, t test.*
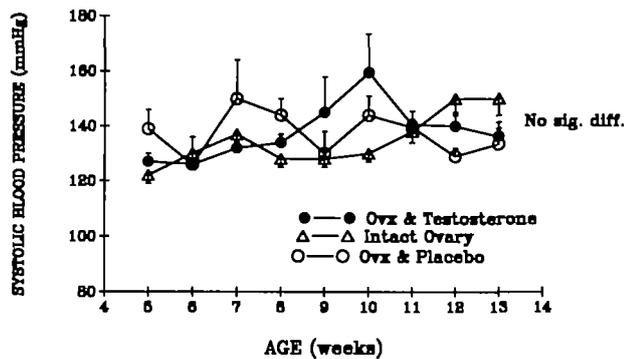
FIGURE 5. *Lme graph showmg systolic blood pressure of female hybnds (testicular femmized male [Tfm] carrier female×spontaneously hypertensive rat male) who have an intact ovary compared with those who were ovariectomized (Ovx) and given testosterone implants or Ovx and given a placebo (mean±SEM). There were no significant differences between groups (two-way analysis of variance)*

testosterone was below the limits of detectability in both castrate groups.

The effects of ovariectomy on blood pressure (experiment 3) can be seen in Figure 5. The majority of pressures over time for all three groups were in the normotensive range, and testosterone administration did not increase blood pressure although at week 10 there was a nonsignificant rise to 158 mm Hg. Plasma testosterone was 0.5 ± 0.5 μg/ml both in the intact and ovariectomized females and was 1.9 ± 0.4 μg/ml in the implant group.

The organ weight comparisons of experiment 1 are seen in Table 1. The Tfm hybrids had significantly larger pituitary glands (161% of normal males, $p<0.01$) and adrenal glands (200% of normal males, $p<0.05$), but smaller testes (33% of normal males, $p<0.001$) when compared with matched normal sibling males. The heart ventricular weights among the three groups did not differ significantly.

The blood chemistries for experiment 1 are reported in Table 2 and show the respective testosterone, norepinephrine, electrolyte, and lipid levels. As expected, the hybrid Tfm animals had higher testosterone levels than the normal hybrid males, which were higher than females, and castrated males were below the limits of detectability. There were no significant differences between male groups in norepinephrine, cholesterol, or electrolytes. The hybrid females had lower testosterone ($p<0.05$) and higher norepinephrine ($p<0.05$) than normal males.

Discussion

In our previous work, we showed that the blood pressure rise in F_1 offspring resulting from a cross of a Wistar-Kyoto (WKY) female with an SHR male required both a Y chromosome component and an autosomal component. The present results support a role for the Y chromosome in transmitting hypertension genes in the SHR rat.[11] The blood pressure observed in the male hybrids (195 mm Hg) was comparable with that of the parent SHR males at 12 weeks of age (190 mm Hg). Since the males of the normotensive Holtzman strain normally have a blood pressure of 155 mm Hg at 12 weeks of age, this suggests that the increase of 40 mm Hg in the hybrid males was due to genes inherited from the SHR fathers. The results further suggest that about 15–20 mm Hg of this 40 mm Hg was due to an androgen receptor effect. The evidence for this is derived from an analysis of the Tfm data. The Holtzman Tfm rat had pressures that were 15 mm Hg lower than the normal Holtzman males at 12 weeks of age (140 versus 155 mm Hg), and the hybrid Tfm animals had pressures that were 25 mm Hg lower than the normal hybrid males at 12 weeks (170 versus 195 mm Hg). The remainder (15 mm Hg) of the 40 mm Hg pressure difference must be accounted for by either non-androgen receptor–mediated effects or by other gene effects. Support for this conclusion can be seen

TABLE 1. Relative Organ Weights of Hybrid Groups (mg/100 g body wt)

Group	Pituitary	Adrenal glands	Testes	Heart ventricles
Hybrid normal males	2.72 ± 0.23	17.6 ± 0.9	710 ± 30	331 ± 23
Hybrid testicular feminized males	$4.53\pm0.1^*$	$34.9\pm1.3\dagger$	$235\pm9\dagger$	311 ± 4
Hybrid females	$4.64\pm0.36^*$	$22.9\pm0.9\ddagger$	NA	339 ± 10

Values are mean±SEM. NA, not applicable
$^*p<0.01$, $\dagger p<0.001$, $\ddagger p<0.05$ compared with hybrid normal males.

TABLE 2. Blood Chemistry of Hybrid Normal Males, Hybrid Testicular Feminized Males, and Hybrid Females

Group	Testosterone (ng/ml)	Norepinephrine (pg/ml)	Cholesterol (mg/dl)	Na$^+$ (meq/l)	K$^+$ (meq/l)	Cl$^-$ (meq/l)
Hybrid normal males ($n=8$)	2.1 ± 0.35	429 ± 50	60 ± 2.1	146 ± 2	6.4 ± 2.8	107 ± 1.2
Hybrid testicular feminized males ($n=9$)	$4.0\pm0.5^*$	383 ± 45	69 ± 2.5	144 ± 2	5.6 ± 1.3	106 ± 0.8
Hybrid females ($n=12$)	0.5 ± 0.5	$601\pm135^*$	61 ± 3	145 ± 2	6.0 ± 2.1	108 ± 0.7

Values are mean±SEM.
$^*p<0.05$ compared with normal males.

in the blood pressure differences between the F_1 hybrid females and the parent Holtzman females. The blood pressure difference between these two strains was also 20 mm Hg (155 versus 135 mm Hg, respectively).

The castration experiments demonstrated that blood pressure could be normalized in the hybrid males from 195 down to 155 mm Hg or about a 40 mm Hg testis-dependent effect. This finding supports the conclusion that the testes are necessary for the blood pressure rise and, combined with the previous observation, suggests that some of the effects of the testes may be due to the action of androgens through non–androgen receptor processes or to some other testis-derived factor. In support of the latter suggestion, blood pressure in the castrated hybrid Tfm rats was lower (23 mm Hg) than that of the gonadally intact hybrid Tfm rats (147 versus 170 mm Hg, respectively) (i.e., even though there were deficient androgen receptors in both Tfm groups, castration lowered the blood pressure). This effect is testis-specific because it did not occur in females that were ovariectomized. Therefore, the mechanism for this decrease may be through another testis-derived factor or through a non-androgen receptor–mediated effect of androgens. A precedent for non-androgen receptor–mediated androgen effects exists. Leiter[22] has shown, in studying the genetics of diabetes susceptibility in mice, that the liver may be androgenized even without functional androgen receptors. In addition, functional androgen receptors were not required to mediate the diabetes promotive action of androgens in genetically obese mice.[22]

One possible testis-derived factor would be estrogen. Testosterone is readily converted to estrogen in the peripheral tissues of both the Tfm and its normal male sibling. In the Tfm, blood estradiol levels are elevated above that of the normal male.[23] However, how estrogen may act on blood pressure in the male in a manner different from that in a female is not yet known.

Also, it is possible that in the hybrid Tfm rats, less deoxycorticosterone is produced than in the hybrid normal males or in SHR, which could reduce the blood pressure. In Dahl salt-sensitive rats, the effects of the *Hyp-1* locus caused a twofold to threefold higher plasma level of 180H-deoxycorticosterone (DOC) than in resistant rats, but the plasma levels of corticosterone and DOC were not different between the strains.[24,25]

Also supportive of this possibility is the fact that the pituitary and adrenal weights of the hybrid Tfm rats were significantly elevated compared with the hybrid male controls, suggesting reduced DOC feedback to these tissues and consequent hypertrophy.

There appears to be a developmental effect on blood pressure that occurs around 10–12 weeks of age. At this time the blood pressure is significantly increased in the hybrid males and in the normal King-Holtzman males and only slightly later at 12–13 weeks in the male SHR. However, this elevation did not occur in females or in the hybrid Tfm rats or in castrated hybrid males. This again underscores the importance of the testes in the pressure rise at this time. For testosterone to influence target organs involved in blood pressure control, nuclear binding needs to be demonstrated. Indeed, Stumpf[26] has shown that dihydrotestosterone binds to blood vessel wall, heart, and central nervous system cardiovascular areas, and castration of SHR males before puberty has been shown to normalize their pressures.[13] Castration also abolished the blood pressure sexual differences in DOC-salt hypertension in Sprague-Dawley rats.[12] Also Cambotti et al[13] reported that the neonatal gonadal hormone milieu contributed significantly to the sexually differentiated pattern of hypertension in the SHR.

Also, Ganten et al[8] have shown that prepubertal administration of androgen receptor blockers in SHR males significantly reduced blood pressure in the adults. However, the same treatments had no effect in old hypertensive rats.[8]

A potential testosterone effect on blood pressure may be through enhanced sympathetic outflow, which can increase blood pressure. Lara et al[27] showed that testosterone modulated norepinephrine storage and release in the sympathetic fibers of the rat vas deferens. Also, there was enhancement of norepinephrine pressor responses in testosterone-treated cats,[28] and Salt[29] showed in testosterone blocker studies (high levels of circulating testosterone) that the norepinephrine uptake-2 mechanism was reduced, thereby increasing plasma norepinephrine, which could influence blood pressure. In addition, androgens may enhance the pressor action of norepinephrine.[28] In our present studies, the resting plasma norepinephrine levels were not different between male groups, but this does not rule out the possibility of regional differences of sympathetic output and regional norepinephrine differences that could affect blood pressure.[30] This interactive influence could be similar to the potentiation of norepinephrine by salt as reported in our animal studies.[31,32]

Also, there may be an interaction between cardiovascular target organs, testosterone, and blood pressure. Lengsfeld et al[33] have reported that gonadectomy and hormonal replacement changes systolic blood pressure and ventricular myosin isoenzyme pattern in SHR stroke-prone rats. They showed that ventricular myosin isoenzyme pattern was under the dominant control of androgens and dissociates the expression of myosin isoenzyme from both blood pressure and cardiac hypertrophy. However, preliminary studies in our laboratory have found no functional differences in isolated left ventricular performance between hybrid Tfm or hybrid normal rats (unpublished observations). This is not to say that testosterone does not produce significant biochemical changes in the heart; indeed, the enzyme changes reported are important in cardiac hypertrophy and heart development. Also, testosterone may alter the ratio of elastin to collagen in resistance vessels,

which could increase resistance and elevate blood pressure.[34]

With regard to the effects of testosterone on female blood pressure, a question arises. If testosterone is developmentally involved in hypertension, then why didn't the females exhibit a pressure rise after ovariectomy and testosterone administration? One explanation could be that the testosterone needs to be present at a critical time before 5 weeks of age. Another possible explanation is that a Y chromosome, which a female lacks, is necessary for the full expression of the developmental effect. For instance, if there is a gene on the Y chromosome that influences steroid metabolism, then just the presence of male levels of testosterone may not be sufficient to cause the blood pressure elevation seen in males. An enzyme regulating the metabolism of testosterone such as steroid sulfatase (STS) may be involved. The gene for STS has been reported both on the X and the Y chromosome in the mouse, but its location in the rat is not known.[22] If the gene is expressed from both the X and the Y chromosomes in males, then it is possible that higher levels of STS would permit more free androgens to androgenize critical tissues, inducing morphological changes that increase blood pressure. Also, our data does not suggest an estrogen protective effect on blood pressure since the ovariectomy group with placebo did not show a blood pressure rise.

In conclusion, blood pressure was lowered in male hybrids with deficient androgen receptors. This could be due to both organizational effects in the central nervous system and peripheral organs during development or due to decreased activational effects in the adult peripheral target organs. Since castration before puberty produced a greater drop in blood pressure than androgen deficiency alone, we conclude that there may be non–receptor-mediated effects of androgens or a testis-derived factor influencing blood pressure. Since blood pressure remained higher in hybrid castrated rats having a normal population of androgen receptors compared with hybrid castrated Tfm rats, we suggest that the androgens have a developmental effect on blood pressure before puberty. Finally, androgens may interact synergistically with the autosomes and the Y chromosome to elevate blood pressure in the male.

Acknowledgments

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