The influence of ethanol (alcohol) consumption on blood pressure during and after the development of hypertension was examined by using spontaneously hypertensive rats (SHR) and stroke-prone SHR (SHRSP). Normotensive Wistar-Kyoto (WKY) rats were also used for comparison. Substituting alcohol (5–20%) for drinking water at 1 month of age retarded the age-dependent rise of blood pressure in all three strains so that, at 7 months, blood pressure measured by a tail-cuff method was 24 mm Hg, 26 mm Hg, and 41 mm Hg lower in the alcohol-treated WKY rats, SHR, and SHRSP, respectively, than in untreated rats. Significant differences in blood pressure were seen in each strain after only 3 months. Withdrawal of alcohol at this stage caused an acute rise of blood pressure then a return to subnormal levels, which persisted for a further 3 months. Administration of 15% alcohol to adult WKY rats and SHR for 2 months had no significant effect on blood pressure. Increasing alcohol content to 20% for a further 2 months prevented rises of blood pressure in both strains. Thus, although continuous drinking of alcohol does not lower blood pressure, it appears to counteract the development of hypertension in rats. (Hypertension 1989;13:607–611)

A link between alcohol abuse and hypertension has long been recognized. However, the risk of cardiovascular disease associated with moderate consumption of alcohol is less clear, and our efforts to understand this relation have been hampered by the limited success of reproducing alcohol-induced hypertension and cardiomyopathy in animal models. We undertook to examine the influence of alcohol consumption on the expression of genetically determined hypertension by administration of alcohol in drinking water to the most widely used animal models of hypertension, spontaneously hypertensive rats (SHR), and the substrate, stroke-prone SHR (SHRSP). In a preliminary study, we found that the development of hypertension was retarded in SHRSP drinking 15% ethanol from weaning. This surprising finding is now confirmed and extended by our present observations in WKY rats, SHR, and SHRSP.

Materials and Methods
Male WKY rats, SHR, and SHRSP were obtained at 1 month of age from our own colony, which was established in 1982 with breeders derived successively from Kyoto University (Kyoto, Japan), National Institutes of Health (Bethesda, Maryland), and Flinders University (Adelaide, Australia) and maintained in accordance with prescribed guidelines. Rats of each of the three strains were randomly allocated to untreated control (C) or alcohol-treated (A) groups, and their blood pressure (BP) was measured on at least two consecutive days by a tail-cuff method. In this procedure, the rats remained at room temperature in perspex restrainers while their tails were gently warmed under an infrared lamp. The pulse was detected by applying a Doppler ultrasound probe with an audible output to the underside of the tail. BP was taken as the average of at least three readings of the pressure in a manually inflated tail cuff when the pulse could first be heard during deflation. A cuff of 1/4 in. diameter was used for rats up to 7 weeks of age, after which a 7/6 in.-diameter cuff was used.

After the initial BP measurements, the drinking water of rats in group A was replaced with 5% alcohol. This concentration was gradually raised to 20% over the next 2 weeks. Body weight and BP were monitored in all rats for 6 months. After 3 months, alcohol was suddenly withdrawn from half of these rats (group W). Measurements were made daily on this group for the next week and then every 2 weeks. After 6 months, rats were killed by decapitation, and hearts were excised and weighed after removal of atria.
In a separate experiment, the effect of alcohol consumption on adult rats with established hypertension was examined. Due to limited availability of male rats, female SHR and WKY rats aged 14–15 weeks were used. After taking initial measurements of tail-cuff BP, the rats were randomly allocated to control or alcohol-treated groups. The latter were given only 15% alcohol to drink for 10 weeks. The concentration was then increased to 20% for a further 10 weeks. BP was regularly monitored in all rats. After 2, 7, and 10 weeks of alcohol treatment, blood samples were taken in the morning by cardiac puncture under light ether anesthesia. The alcohol concentration in 0.1-ml aliquots of these samples was determined by a gas chromatographic method with n-propanol as an internal standard.11

Results

The progressive rise of BP with age in the weanling WKY rats and SHRSP used in this study is shown in Figure 1. BP rose sharply in the first 2 weeks in WKY rats then reached a plateau, with a very gradual rise of less than 5 mm Hg per month occurring subsequently. In SHRSP, however, BP continued to rise sharply for several months, and the slope was always steeper than that for WKY rats. A similar but less pronounced rise was seen in the SHR. BP data for SHR at 4 and 7 months of age appear in Table 1.

The rise of BP in rats drinking alcohol (A) was less than that of the untreated rats (C). This was evident in all three strains but especially in the SHRSP, where the rate of rise is generally greatest. At 4 months of age, when the BP of group A was significantly lower than that of group C for each strain (see Table 1), half of the rats were withdrawn from alcohol (group W). There was a sudden rise of BP in these rats, peaking at 2–3 days after withdrawal. For clarity, only the readings taken 2 and 4 days after withdrawal have been plotted in Figure 1. Within 2 weeks, the BP of these rats had fallen to levels comparable with rats continuing on alcohol. Despite considerable fluctuation, BP in the withdrawn groups remained significantly lower than that of the untreated rats for the next 3 months (Figure 1 and Table 1).

Substitution of alcohol for drinking water suppressed food and fluid intake to a similar extent in the three strains. Fluid intake, measured weekly and averaged over all rats, is plotted in Figure 2. The immediate reduction in intake was followed by a retardation of growth, notably in the SHRSP, as shown in Figure 3. Body weight data for the other strains appear in Table 1. Replacement of alcohol with water at 4 months of age resulted in a massive increase of drinking followed by a return to normal levels. This replacement was accompanied by a greater increase of growth, so that body weight in SHRSP also reverted to normal. Table 1 also shows the weights of hearts taken from the rats at 7 months of age. Heart weight in SHRSP, which was slightly but not significantly greater than in WKY rats, was also reduced by alcohol treatment but restored after alcohol withdrawal. No gross pathological changes were seen in any of the treated rats.

To see whether the antihypertensive effect of alcohol occurred only during development, a separate experiment was undertaken with WKY rats and SHR at 14–15 weeks of age. Tail-cuff BP for these rats is plotted in Figure 4. Hypertension was established in the SHR, with their average BP at least 30 mm Hg higher than in WKY rats. Half of the rats in each strain were given 15% alcohol to drink for 10 weeks. This treatment had little effect on BP, so the alcohol concentration was increased to 20%. Within 4 weeks, there was a significant difference in BP between alcohol and control groups in each strain, and the difference again was greater in the hypertensive rats.

Due to their nocturnal drinking behavior and rapid clearance of alcohol, early morning measurements of blood alcohol concentration in these rats were highly variable. Values obtained for WKY rats and SHR were, respectively, 19±6 and 16±8 mg/dl after 2 weeks, 29±8 and 38±21 mg/dl after 7 weeks, and 28±8 and 14±5 mg/dl after 20 weeks of treatment. Values represent mean±SEM from six rats in each case. It is evident that, even though increasing the alcohol concentration of the drinking water from 15% to 20% amplified the effect of alcohol treatment on BP, it did not cause an increase in blood alcohol levels.

Discussion

The observations reported above on tail-cuff BP in rats receiving alcohol from an early age confirm

![Figure 1](link-to-figure)

**Figure 1.** Line graph showing effect of alcohol on rise of blood pressure (BP) with age in Wistar-Kyoto (WKY) rats and stroke-prone spontaneously hypertensive rats (SHRSP). BP development is shown for rats drinking water (C) or 20% alcohol (A) from 1 to 7 months of age. Half of the alcohol-treated rats were given water only (W) to drink after 3 months (arrow). Points represent mean±SEM of tail-cuff BP in each group of rats (numbers per group appear in Table 1). At several points, SEM is so small that it is obscured by symbol.
TABLE 1. Body Weight, Heart Weight, and Tail-cuff Blood Pressure in Wistar-Kyoto Rats, Spontaneously Hypertensive Rats, and Stroke-prone Spontaneously Hypertensive Rats

<table>
<thead>
<tr>
<th>Age</th>
<th>Body weight (g)</th>
<th>Heart weight (g)</th>
<th>Tail-cuff BP (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4 mos</td>
<td>7 mos</td>
<td>7 mos</td>
</tr>
<tr>
<td>WKY</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>351±10 (8)</td>
<td>397±9 (6)</td>
<td>1.26±0.06 (9)</td>
</tr>
<tr>
<td>A</td>
<td>318±9* (14)</td>
<td>373±12 (6)</td>
<td>1.16±0.02 (10)</td>
</tr>
<tr>
<td>W</td>
<td>. . . (7)</td>
<td>411±6 (6)</td>
<td>1.27±0.07 (11)</td>
</tr>
<tr>
<td>SHR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>321±10 (6)</td>
<td>366±15 (6)</td>
<td>1.23±0.08 (12)</td>
</tr>
<tr>
<td>A</td>
<td>329±6 (10)</td>
<td>402±6 (5)</td>
<td>1.32±0.04 (13)</td>
</tr>
<tr>
<td>W</td>
<td>. . . (5)</td>
<td>385±4 (5)</td>
<td>1.41±0.03 (14)</td>
</tr>
<tr>
<td>SHRSP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>331±4 (8)</td>
<td>361±2 (6)</td>
<td>1.40±0.05 (15)</td>
</tr>
<tr>
<td>A</td>
<td>269±9* (12)</td>
<td>327±29 (6)</td>
<td>1.18±0.09* (16)</td>
</tr>
<tr>
<td>W</td>
<td>. . . (6)</td>
<td>369±13 (6)</td>
<td>1.50±0.12 (17)</td>
</tr>
</tbody>
</table>

Values represent mean±SEM. Numbers in parentheses indicate rats remaining in each treatment group at each age. BP, blood pressure; WKY, Wistar-Kyoto rats; C, group given drinking water only; A, group given 20% alcohol for 6 months; W, group given 20% alcohol for 3 months followed by water for 3 months; SHR, spontaneously hypertensive rats; SHRSP, stroke-prone SHR.

*Significantly different from group C (p<0.05, Student's t test).

our preliminary observations of the effect of alcohol on BP in WKY rats and SHRSP. Unlike the early findings of Chan and Sutter, who reported that the addition of 20% alcohol to drinking water increased BP in normotensive WKY rats, we found that BP is lower in both normotensive and hypertensive strains of rats drinking alcohol.

We were disturbed by our preliminary finding in SHRSP, because we had reasoned that administration of 15% alcohol to young rats with a genetic predisposition to hypertension in a manner similar to that which raised blood pressure in normotensive rats would be likely to exacerbate the development of hypertension. Wondering whether this discrepancy might have been due to the concentration of alcohol used or to the age or duration of treatment, we chose to use 20% alcohol and to treat adult as well as weanling rats in the present experiments. Since that time, however, the studies by Sanderson et al and Jones et al in SHR have shown that chronic consumption of 20% alcohol results in lower BP in rats of this strain, and an earlier report by Khetarpal and Volicer showed administration of 10% alcohol did not significantly affect BP in either WKY rats or SHR. It seems unlikely, therefore, that our inability to obtain a pressor effect was due to use of an insufficient concentration of alcohol. In fact, recent comments by Chan et al and Pang et al cast doubt on their ability to reproduce the pressor effect of alcohol in normotensive rats obtained from a different source.

It is significant that alcohol administration has not been shown to actually lower BP in any strain of rat. It appears that its antihypertensive effect is to resist the normal age-dependent rise of BP. Since the rate of rise diminishes in rats, as in humans, at
A greater retardation of BP is achieved by administration of alcohol from an early age. The mechanism of this antihypertensive effect and its relation to the postulated pressor effect of alcohol in humans is uncertain.

Unlike humans, rats show an aversion to alcohol. This was reflected in the lower fluid intake of the rats drinking alcohol, which might cause BP to be lowered through chronic dehydration. This possibility has been addressed in a study where young SHR were given 20% alcohol for 6-9 months but also drank water intermittently. Alcohol still suppressed the development of hypertension in these rats. Moreover, preliminary measurements in other rats showed that plasma volume is unaffected by chronic alcohol treatment (unpublished observation). Another possibility is that growth retardation caused by early administration of alcohol, particularly in SHRSP, prevents the normal rise of BP with age. However, smaller increases of body weight with age can also be associated with accelerated development of hypertension, as seen with salt loading in SHR.13

The acute rise of BP elicited by sudden withdrawal of alcohol resembles the withdrawal hypertension reported in alcoholics.14 How acute consumption,15 chronic consumption,16 and withdrawal of alcohol can all elevate BP in humans is not clear. However, in the rat, it is likely that the antihypertensive effect of chronic alcohol consumption and the acute pressor effect of sudden withdrawal are mediated by different mechanisms, since, in agreement with our preliminary study, the former effect was more pronounced in the hypertensive strain, whereas the withdrawal hypertension was more severe in the normotensive rats.

Our most significant finding is that, despite any adverse effects seen during the period of alcohol consumption, normal fluid intake and body weight are restored once alcohol administration is discontinued, but the lower level of BP established during alcohol treatment persists at least 3 months longer. This demonstration of a sustained antihypertensive effect induced in rats by a simple dietary intervention is unique. Regardless of our inability to reproduce the so-called pressor effect of alcohol in humans,16 we have presented an experimental model that could help not only to elucidate the pathogenesis of spontaneous hypertension in rats but also to identify mechanisms by which certain drugs might be able to counteract the early development of hypertension in genetically predisposed individuals.

References


Figure 3. Line graph showing effect of alcohol consumption on body weight in stroke-prone spontaneously hypertensive rats (SHRSP). Mean±SEM of body weight measured at 2-week intervals from 1 to 7 months of age is shown for SHRSP drinking water (C), 20% alcohol (A), or withdrawn from alcohol (W) and given water only to drink after 3 months (arrow). At several points, the SEM is so small that it is obscured by the symbol.

Figure 4. Line graph showing effect of alcohol in rats with established hypertension. Mature (14–15-week-old) Wistar-Kyoto (WKY) rats and spontaneously hypertensive rats (SHR) were given 15% alcohol (——) to drink for 10 weeks followed by 20% alcohol for a further 10 weeks. Control rats (———) drank water only. Points are mean±SEM of tail-cuff blood pressure (BP) (n=6 in each case).

**KEY WORDS**  • alcohol • blood pressure • spontaneously hypertensive rats
Antihypertensive effect of alcohol in spontaneously hypertensive rats.
P R Howe, P F Rogers and R M Smith

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