THE EFFECT OF THIAMINE TETRAHYDROFURFURYL DISULFIDE (TTFD) ON BLOOD PRESSURE IN SPONTANEOUSLY HYPERTENSIVE RATS (SHR)

Thirty age matched male rats of the Kyoto spontaneously hypertensive strain (SHR) were housed in individual stainless steel cages. Their weights respectively were between 130 and 223 grams. There were 5 deaths early in the experiment, thought to be due to overheating of the animals before taking the tail blood pressure. Two of these deaths occurred in the randomly selected treatment group, and 3 in the control group. The experiment was subsequently completed with 13 in the treated group and 12 in the control group. The dose of TTFD was calculated by assessing the average approximate 24 hour intake of water per rat and adding an aqueous colorless solution of TTFD to the drinking cup of each rat in the treated group. Taste did not seem to influence the intake of water by treated animals compared with controls.

Body weight and blood pressure were recorded twice a week by a technician who was unaware of which rats were receiving TTFD. After a warming period in a heating box, pressures were recorded by the tail cuff method at approximately the same time of day. The same technician performed all necessary procedures throughout the experiment. After an initial period of adjustment, the blood pressure of all animals appeared to be relatively stable and the experiment was commenced.

An initial dose of 5 mg. of TTFD a day was given from April 8th. to May 31st. It was then increased to 7.5 mg. Thereafter the dose was increased at intervals. On June 16th. it was raised to 10 mg., to 12.5 mg. on July 9th. and 15 mg. on July 22nd. From July 22nd. to August 11th. both groups were given a supplement of 3 mg. of calcium carbonate and 1.5 mg. of magnesium oxide each. These supplements were also added to drinking cups. The entire experiment covered a period of four months.

RESULTS

The mean blood pressure of each group of rats is shown in figure 1. Blood pressure of a single rat whose response appeared to be definite (Fig 2) are
contrasted with one who was treated but did not respond (Fig 3) and an untreated control (Fig 4). All 25 records were reviewed blindly and individually, without knowing which group each animal represented. The correct assessment was made in 21. Of the 4 records which were assessed incorrectly, three were from TTFD supplemented animals that had blood pressure similar to the controls. One record from a rat in the control group appeared to be similar to that seen in a TTFD responsive animal.

Of the 13 TTFD supplemented rats, 5 showed a response that appeared to be definite, and the records were similar to that seen in Figure 2. Blood pressures in these responders were much the same at the end of the experiment as at the beginning, whereas controls and non responders showed a rise of approximately 20 to 25 mm. Hg. Some TTFD supplemented animals who failed to show a definite response revealed greater lability in their week to week pressures, but this was too variable to use as a distinguishing feature.

Figure 1

[Graph showing blood pressure over time with labeled axes]

Mean blood pressure of TTFD treated SHR rats compared with untreated controls.
Statistical Analysis

There was no difference in mean blood pressure readings between the 2 groups through *April and May*. On May 31st. the dose increases began and 2 subsequent periods were analyzed separately: **period A from May 31st. to July 7th., and period B from July 12th. to August 22nd.** In both of these time periods, using a repeated measures analysis, there was a statistically significant difference between the two groups. For period A the *P value was < .05* and for **period B < .01**. Although the two sample histograms overlapped, the sample means were clearly different, particularly when compared with readings before May 31st. This difference was maintained throughout the duration of each time period. Consequently, in terms of average response differences, there was statistical significance between the groups. Each bar represents the mean blood pressure for the group, plus or minus two standard deviations. It is felt that this is an honest portrayal in view of the amount of blood pressure lability noted in individual animals.

**FIGURE 2**

Record of blood pressures obtained in a single SHR rat treated with TTFD. This record was typical of only 5 of 13 treated animals.
Record of blood pressures obtained in a single SHR rat treated with TTFD who failed to show a response. Note the unusual lability in the week to week pressure.

FIGURE 3

Typical tracing of blood pressures obtained in an untreated control SHR rat. Lability in the pressures recorded week to week is not as great as in those shown in a treated non-responder.

FIGURE 4
DISCUSSION

The results show that TTFD does have a biologic effect on blood pressure in some of these genetically abnormal rats, in whom the neurogenic initiating influences are reportedly similar to those in human hypertension (1). This effect appears to be either time or dose related, and might be a mixture of both variables. The mechanism is conjectural, but might be hypothesized from what is known about the action of TTFD. Some evidence suggests that it stimulates cholinergic action and has a therapeutic effect due to factors other than simple replacement of a thiamine deficiency (2). It has also been suggested that the hypertensive mechanism in SHR is adrenergic in nature (3). It is therefore hypothesized that the antihypertensive effect of TTFD in this rat experiment was due to its stimulation of cholinergic action to a point where it produced a homeostatic balance against the genetically determined adrenergic dominance. Increased autonomic nervous drive has been suggested in hypertension, heart failure and diabetes (4).

It seems clear that there is good reason to study the pharmacologic effects of TTFD further. It is well established as a useful therapeutic agent in Japan and in other parts of the world. No toxic effects have been observed in the treatment of human subjects or in animals at average therapeutic doses. It would be very safe to use TTFD rather than a sympathetic blocker on a trial basis in essential hypertension.


