Research

Chronic, Severe Hypertension Does Not Impair Spatial Learning and Memory in Sprague-Dawley Rats

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This study tested the hypothesis that long-term hypertension impairs spatial learning and memory in rats. In 6-wk-old Sprague-Dawley rats, chronic hypertension was induced by placing one of three sizes of stainless steel clips around the descending aorta (above the renal artery), resulting in a 20–80-mm Hg increase of arterial pressure in all arteries above the clip, that is, the upper trunk and head. Ten months later, the rats were tested for 5 d in a repeated-acquisition water maze task, and on the fifth day, they were tested in a probe trial; that is, there was no escape platform present. At the end of the testing period, the nonsurgical and sham control groups had similar final escape latencies (16 ± 4 sec and 23 ± 9 sec, respectively) that were not significantly different from those of the three hypertensive groups. Rats with mild hypertension (140–160 mm Hg) had a final escape latency of 25 ± 6 sec, whereas severely hypertensive rats (170–199 mm Hg) had a final escape latency of 21 ± 7 sec and extremely hypertensive rats (>200 mm Hg) had a final escape latency of 19 ± 5 sec. All five groups also displayed a similar preference for the correct quadrant in the probe trial. Together, these data suggest that sustained, severe hypertension for over 10 mo is not sufficient to impair spatial learning and memory deficits in otherwise normal rats.

Whereas in the early part of the twentieth century clinicians believed that essential hypertension was necessary for normal physiological function (i.e., it was essential), more recent studies have clearly demonstrated the deleterious nature of chronic elevation of arterial pressure on many organ systems. Nearly 25 yr ago, data from Wilke and Eisdorfer suggested that hypertension may lead to memory impairments (Wilkie et al. 1976), and many subsequent reports have supported this relationship in humans (e.g., Franceschi et al. 1982; Waldstein et al. 1991; Elias et al. 1993, 1997; Swan et al. 1998); however, it remains unclear whether memory deficits and hypertension are causally related or simply coexist. Several additional studies suggest that high blood pressure contributes to cognitive deficits in aging individuals (e.g., Elias et al. 1995; Skoog 1997), but other research indicates that cognitive function gradually declines with age in humans, irrespective of arterial pressure (e.g., Beatty 1988; Albert 1993) and that this age-related impairment extends to spatial learning and memory tasks (Sharps and Gollin 1987; Petersen et al. 1992). The interpretation of these findings is complicated by the fact that the decline in learning and memory varies widely in aging (e.g., Albert 1993) and hypertensive humans (e.g., Pentz et al. 1979). The presence of other diseases within these individuals (e.g., type 2 diabetes; Elias et al. 1997) further obscures the interpretation.

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Whereas the hypothesis that hypertension affects learning and memory can be more easily tested in animals, few animal studies have been undertaken to clarify the relationship caused by the lack of appropriate models. Such animal models (e.g., Meneses and Hong 1998a) are important for defining the contribution of hypertension to memory impairments and for assessing the ability of antihypertensive drugs to improve or worsen the memory deficits in hypertensive individuals (e.g., Prince et al. 1996; Meneses and Hong 1998b). Several studies suggest that various antihypertensive drugs affect memory and learning (Lasser et al. 1989; Bulpitt and Fletcher 1992; Wyss and Van Groen 1994).

We have demonstrated previously that in comparison to young rats, 12-mo-old Sprague-Dawley rats (SD) are unimpaired in the acquisition of an eight-arm radial maze task. In contrast, 12-mo-old spontaneously hypertensive rats (SHR) demonstrate a marked deficit in this task (Wyss et al. 1992) and in a water maze task (Wyss et al. 2000). Further, we have demonstrated that chronic antihypertensive treatment of SHR nearly normalizes memory in the 12-mo-old SHR. Similar deficits in SHR have recently been demonstrated by other researchers using similar tasks (Meneses et al. 1996; Gattu et al. 1997a,b; Meneses and Hong 1998b). Learning deficits have also been reported in other hypertensive rodent models of hypertension, including genetic (e.g., Hirawa et al. 1999) and induced (e.g., Meyer et al. 1998) models. But the interpretation of these data is complicated. In normotensive rats, learning and memory decline with increasing age, albeit at a somewhat later age,

18–24 versus 12 mo of age (Wyss et al. 2000), and whereas antihypertensive medications often improve learning in hypertensive models, they also improve learning in normotensive controls (e.g., Hirawa et al. 1999).

Whereas some of these data suggest that hypertension may accelerate or even precipitate memory disorders especially in otherwise compromised animals, there is little direct evidence as to the independent contribution of hypertension to such learning and memory impairments. For instance, SHR, compared with SD, are differentiated by many physiological and hormonal dissimilarities that are only weakly related to the differences in arterial pressure regulation, for example, they are hyper-reactive and hyperactive (Hendley and Ohlsson 1991; Hendley et al. 1992). In this study, we tested the interactions between hypertension, age, and spatial learning and memory in 12-mo-old SD in which chronic hypertension was induced by aortic coarctation. This study tests the hypothesis that in 12-mo-old SD, 10 mo of chronic, severe hypertension impairs spatial learning and memory.

RESULTS

Animals

All rats tested in the experiments were healthy, displaying no obvious physical impairments (e.g., glaucoma, cataracts, respiratory disease, motor dysfunction, or tumors) that would have interfered with behavioral testing. The group of animals with the 0.76-mm-diameter clips had a carotid mean arterial pressure (MAP) of 132 ± 2 mm Hg, which was higher than the carotid MAP of the sham and nonsurgical controls (107 ± 5 and 108 ± 5 mm Hg, respectively; Table 1), that is, they were moderately hypertensive (ModHyp). The smaller clips on the other two groups resulted in severe hypertension. The 0.62-mm-diameter clip group had a carotid MAP of 183 ± 10 mm Hg. Three animals in this group died prematurely, and four rats in the group were sacrificed at 10 mo of age for determination of their carotid MAP (179 ± 7 mm Hg). The other rats in this group completed the behavioral testing. Ten out of the 20 animals in 0.56-mm-diameter clip group died prematurely, between 10 and 12 mo of age; therefore only 10 animals from this group were included in the behavioral testing. The carotid mean arterial pressure in this group at that age was 172 ± 12 mm Hg. Our original design was based on the assumption that

carotid arterial pressures were closely correlated with clip size; however, clip size and arterial pressure were not tightly correlated. Therefore, the animals in the last two groups were combined and subdivided into two groups on the basis of their arterial pressures, that is, a very hypertensive group (carotid systolic arterial pressures of 170–199 mm Hg [carotid MAP 167 ± 3 mm Hg]; HiHyp) and an extremely hypertensive group (carotid systolic arterial pressures of >200 mm Hg [carotid MAP 192 ± 4 mm Hg]; ExHyp). Femoral MAP in ExHyp rats was 124 ± 6 mm Hg. It should be noted that both the HiHyp and ExHyp groups had significantly increased heart weight/body weight ratios (Table 1). All groups displayed rapid growth between birth and 4 mo of age, and there were no differences in body weight among the five groups at 12 mo of age (Table 1).

Gross inspection of the brains did not reveal overt changes (e.g., tumors or lesions) in any group. The density of cortical neurons, the cholinergic innervation of the cortex, and the blood supply to the hippocampal formation were not visibly altered when inspected at 200 $\times$ magnification.

Behavior

Between the five groups of rats, there were no significant differences in swim speed (Table 1; $F(4,35) = 1.10$). The performance (i.e., the escape latency) of the Control, Sham, ModHyp, HiHyp, and ExHyp rats in the initial week of behavioral testing were nearly identical (Fig. 1, between group $F(4,35) = 2.11$, ns; Group $\times$ Days interaction $F(16,35) = 1.11$, ns; Group $\times$ Trials interaction $F(12,35) = 1.12$, ns), and the performance of each of the five groups improved similarly across days (overall trials effect $F(4,35) = 43.4$, $P < 0.01$; Days effect $F(4,35) = 59.6$, $P < 0.01$). All groups responded to the daily change of the platform position in a similar manner; that is, trial 1 had the longest latency on each day (Figs. 1, 2). This effect was most clear in the Control and ModHyp animals. The learning curves were similar for all groups, and the final escape latencies were not significantly different between groups (Fig. 1). All groups learned the water maze task equally well, as shown in the comparison of escape latencies in the first trial (trial 1) versus the mean of the second and third trial (trial 2/3) of each day (Fig. 2). All five groups improved on both measurements across days. As a measure of working memory in this task, the improvement from trial 1 to trial 2/3 of the

Table 1. Body Weight, Heart Weight, and Blood Pressure

Group	Control n = 8	Sham n = 8	ModHyp n = 8	HiHyp n = 8	ExHyp n = 8
BW (g)	494 ± 15	497 ± 20	518 ± 15	509 ± 13	505 ± 12
Carotid MAP (mm Hg)	116 ± 3	112 ± 5	139 ± 5	167 ± 6	187 ± 7
HW/BW ratio $\times 1000$	3.47 ± 0.31	3.55 ± 0.23	3.46 ± 0.28	3.95 ± 0.19	4.27 ± 0.13
Swim speed (m/min)	13.94 ± 1.44	13.86 ± 1.42	13.79 ± 1.39	14.02 ± 1.45	13.98 ± 1.43

Figure 1 Four graphs to demonstrate the latency (mean and standard error) to escape onto the hidden platform in SD that were normotensive controls (nonsurgical control, closed circle; sham, open circles) and the three groups of hypertensive SD (moderate, Mod; high, Hi; and extreme, Ex). The position of the escape platform was changed before trials 5, 9, 13, and 17.

same day (i.e., the area between the two curves in each graph of Fig. 2) was calculated for each animal. There were no significant differences between groups in this measure. As an overall test of the hypothesis that chronic hypertension impairs learning and memory, the latencies on the final trial were compared to the mean arterial pressure for all rats (i.e., with all animals included); the two measures were not correlated ($r^2 = 0.03$; Fig. 3). Further, there was no significant correlation between these parameters within any group.

In the probe trial (i.e., no escape platform present), all five groups demonstrated a significant preference for the correct quadrant (Fig. 4). All groups displayed similar swimming patterns; for example, looping size, strategy, and frequency of turns. None of the animals displayed thigmotaxis or any obviously abnormal swim pattern.

After a week's rest from the task, the Control and ExHyp groups were tested for a second week in the same paradigm (the other three groups were not tested in a second session). In the second week, the two groups performed very similarly, and there were no differences between the groups in their pattern of learning, final latencies to escape, or probe trial performance (Figs. 5, 6; Group effect week 2; $F(1,15) = 0.73$, ns; Trial and Day effects $F(3,15) = 8.5$, $P < 0.01$; $F(4,15) = 3.5$, $P < 0.01$, respectively.) No interactions were significant).

DISCUSSION

In contrast to several clinical and animal studies suggesting that chronic hypertension impairs learning and memory, the present data demonstrate that chronically hypertensive SD are unimpaired in learning a complex, spatial water maze task. The lack of a significant effect of hypertension on task performance in this study does not appear to be attributable to any bias introduced by the grouping of the animals on the post hoc basis of their arterial pressures. Reanalysis on the basis of the original clip sizes also demonstrates no significant differences between groups. More strikingly, there is no significant correlation between carotid MAP and the latency on the final trial (neither in individual groups analyzed separately nor in the rats analyzed as a whole). This demonstrates that, at least for SD, chronic hypertension has little, if any, detrimental effect on spatial learning and memory (Fig. 3). Together, these data suggest that severe, chronic hypertension (i.e., systolic arterial pressure >200 mm Hg for >10 mo) does not by itself cause a significant impairment of spatial learning and memory, at least in otherwise normal rats. It should be noted that spontaneously hypertensive rats at this age (12 mo) have a systolic arterial pressure of 194 ± 4 mm Hg (Wyss et al. 2000).

The chronic hypertension in the SD rats does not compromise motor behavior, nor does it appear to affect their general health (except for the cardiovascular function). The rats all gained weight at about the same rate and swam at similar speeds. Although several animals died before testing in the group with the smallest clips, the remaining rats in that group showed no gross signs of disease and performed as well as controls in the behavioral task. Further, pilot experiments for this study demonstrate that in SD, the present clipping protocol consistently results in a rapid increase in carotid arterial pressure, which reaches near maximal levels after ~ 1 mo and continues at approximately that level for the ensuing 9 mo.

It is possible that the method for testing in this study is not sensitive to a mild effect of the hypertension on behavior. While this possibility can not be excluded, previous results from this laboratory and others suggest that this relatively difficult task is very sensitive to small differences between groups (Frick et al. 1995; Wyss et al. 2000). For instance, learning of this task is impaired in aged rats (12–24 mo of age), and this impairment proceeds at different rates in the three different strains we have previously tested; that is, SD, SHR, and Wistar Kyoto rats (Wyss et al. 2000). Further, using the task, we have been able to demonstrate the protective effect of antihypertensive therapy on the age-

Figure 2 Line graphs to demonstrate the performance of the five groups of SD on trial 1 (solid lines) and trial 2/3 (broken lines) across the 5 d of training. The closed circles in the upper-left panel indicate the behavior of the control SD, and the open circles indicate the performance of the Sham SD. The linear correlations relating escape latencies (on trial 1 and 2/3) to days were significant for all groups.

related learning impairment in SHR, and the task is sufficiently sensitive to differentiate between the behavioral effects of small selective lesions of each of the anterior thalamic nuclei (Van Groen et al. 1996). It should be noted that the performance of all five groups of SD in this study is very similar to that of 4- and 12-mo-old SD (and very different from the marked impairment of 24-mo-old SD) in our previous studies (Wyss et al. 2000). Thus, if chronic hypertension causes spatial learning deficits in SD, the impairment is likely to be very small, that is, below the detection ability of this sensitive task.

Overall, spatial memory tasks are very sensitive to age-related changes in learning and memory. In humans and rats, age-related memory and learning impairments are often first detectable in relatively complex tasks that require the individual to use spatial environmental information (Beatty 1988; Gallagher and Rapp 1997). Nondemented, elderly (compared to young) subjects are impaired in spatially lo-

cating familiar objects in the environment (Pedzek 1983), and they are also impaired in their ability to identify the location at which a photograph of a familiar scene was taken (Light and Zelinski 1983). Rats display a similar decrease in spatial abilities with age; compared with young adult rats, aged rats are more impaired in water maze, holeboard maze, and eight-arm-radial maze tasks (for review, see Gallagher and Rapp 1997). Thus, complex spatial learning and memory tasks discriminate well between impaired and unimpaired individuals.

Much of the impetus for this study arises from our earlier findings that at 12 mo of age, SHR display a significant impairment of learning and memory and that this deficit is prevented by continuous antihypertensive therapy with an angiotensin-converting enzyme inhibitor (Wyss et al. 1992; see also Gattuti et al. 1997a,b; Meneses and Hong 1998b). Further, compared with young SHR, 26–50-wk-old SHR are very impaired in performing a learned escape response (Hecht et al. 1978). Similarly, in three other hypertensive rat models (i.e., Dahl [Hirawa et al. 1999], mREN [Wilson et al. 1996], and nitric oxide synthase inhibited [Faria et al. 1997]), hypertension is related to an impairment in spatial learning, and antihypertensive medication tends to prevent these impairments in several of these models (e.g., Meneses et al. 1997; Hirawa et al. 1999; but see also Prince et al. 1996). It should be noted that in most hypertensive models, the brain is relatively well protected from the excess arterial pressure by very sensitive autoregulatory

mechanisms, but even in those cases in which autoregulation is fully competent, hypertension can induce vascular changes that alter cerebral blood flow and could thereby contribute to cognitive dysfunction (see, e.g., Jennings et al. 1998). These and other animal studies support the hypothesized causal linkage between hypertension and memory impairment.

In humans, hypertensive patients display decreased performance on the Wechsler Intelligence Test (Wilkie et al. 1976) and in several memory tests (Mazzucchi et al. 1986). Further, Schmidt et al. (1991), have shown that in middle-aged individuals, hypertension is associated with a decline in learning and memory but not in vigilance, attention, or reaction time. This decline in memory is associated with a relatively high frequency of white-matter lesions, suggesting that the cognitive decline in these patients is related to subtle, hypertension-related, vascular damage in the brain (Schmidt et al. 1991). In aged humans, hyperten-

Figure 3 In an analysis across all groups, there was no significant correlation between carotid arterial pressure and latency on the final trial (i.e., trial 20 on day 5) of the first week of testing. Dashed line indicates best fit ($r^2 = 0.03$; ns).

sion is similarly associated with white-matter lesions (van Swieten et al. 1991). Together with the animal studies, this suggests that hypertension may contribute to age-related memory disorders. However, other human studies have suggested that the relationship should be qualified. Cosi and Romani show that several health-related deficits can contribute to learning impairments in elderly patients, but none of these, including hypertension, has a very strong independent contribution (Cosi and Romani 1996). Palombo et al. (1997) have shown that the deficits in hypertensive patients tend to be attentional rather than strictly cognitive, and Elias et al. (1997) demonstrated that the memory deficits in hy-

Figure 4 Bar graphs to demonstrate the time spent in each of the four quadrants of the water maze during the 60-sec probe trial that followed trial 20 in the five groups tested. C (correct) indicates the position of the escape platform on trial 20; L, R, and A indicate the quadrant to the left, right, and across, respectively. An asterisk indicates a significant preference for a quadrant.

Figure 5 Two graphs to demonstrate the performance of the control and ExHyp groups during the first and second week of training. There were no overall differences in the learning pattern between these groups during either week.

pertensive type 2 diabetic patients are primarily caused by a synergy between the two diseases and not to the independent contribution of either disease. Further, the contribution of hypertension to cognitive deficits may be strongly influenced by genetic factors (Manly et al. 1998). Thus, while clinical studies continue to suggest a relationship between hypertension and learning and memory impairments, the independent contribution of hypertension to memory dysfunction is unclear.

These findings do not exclude a contribution of hypertension to cognitive dysfunction; they only demonstrate that chronic hypertension is not sufficient to induce learning and memory impairments. It is very likely that in compromised animals and humans, hypertension can contribute to disturbances in spatial learning. For instance, in SHR, several hormone and physiological systems are compromised (e.g., McCarron et al. 1994; Reid 1994; Kett et al. 1996; Oparil et al. 1996; Aitman et al. 1998; Chalmers 1998), and in such a setting, hypertension may cause con-

Figure 6 Two bar graphs to demonstrate the time spent in each of the four quadrants of the water maze during the 60-sec probe trial that followed trial 20 on weeks one and two of training in Control and ExHyp SD. C indicates the position of the escape platform on trial 20; L, R, and A indicate the quadrant to the left, right, and across, respectively. An asterisk indicates a significant preference for a quadrant.

siderably greater vascular damage in the brain, impairing cerebral blood flow and thereby decreasing cognitive functions. Similarly, in humans, hypertension may augment the cognitive impairments caused by coexisting diseases; for example, Alzheimer's disease, multi-infarct dementia, diabetes, and Parkinsonism. Further, in individuals with selective reductions in cerebral blood flow, hypertension could lead to regional impairments in nutrient and oxygen delivery to the brain (Jennings et al. 1998). Thus, any relationship between hypertension and memory impairments is likely complex and must be considered in light of other contributing factors.

In summary, chronic hypertension is not sufficient to cause spatial learning and memory impairments in SD. Together with our previous data and that of others, we suggest that simple uncomplicated hypertension, even though severe in degree, does not remarkably alter brain structure or cognition, but when hypertension coexists with compromised function in the brain or elsewhere, then hyperten-

sion may consort with the other disease state(s) to impair cognitive function.

MATERIALS AND METHODS

Animals

Five-week-old, male SD rats (Harlan) were housed two to three per cage, at constant humidity ($60\% \pm 5\%$), temperature ($22^\circ \pm 1^\circ\text{C}$) and light cycle (0600–1800 h). Following surgery, all animals (including controls) were housed individually. At 6 wk of age, a hemostatic clip was placed on the descending aorta of 48 of the rats to induce chronic hypertension in the arteries supplying those parts of the body above the clip (i.e., including the head and brain). Arterial pressure below the clip remained normotensive. The rats were anesthetized with sodium pentobarbital (Nembutal; i.p., 40 mg/kg) and placed on a heating pad. The skin above the abdomen was shaved, and an incision was made in the skin and underlying muscle. The peritoneal covering was opened and the intestines gently pulled to the side until the descending aorta was visualized. A stainless steel hemoclip (E. Weck) was placed with an applying forceps (E. Weck) onto the descending aorta just above the renal artery. The intestines were replaced, the wound was sutured, and the animal was allowed to recover. One group of animals ($n = 10$) received hemoclips with an open area of 0.76 mm^2 , the second group ($n = 18$) received hemoclips with an open area of 0.62 mm^2 , and the third group ($n = 20$) received hemoclips with a 0.56 mm^2 opening.

In 10 sham-surgery SD, the above protocol was followed, but a very large clip (open area $> 1.0 \text{ mm}^2$) was placed on the descending aorta; this clip size did not cause a significant obstruction of blood flow in the aorta. A fifth group of 10 SD served as nonoperated controls. All protocols for the animal experiments were approved by the University of Alabama at Birmingham's Institutional Animal Care and Use Committee and were in accordance with the NIH guide on the humane treatment of experimental animals.

Behavior

Spatial learning was tested in an open-field water maze, similar to that developed by Morris (1984). Our version of the maze consists of a large round tank (183 cm diameter, 60 cm high) of clear water ($22^\circ \pm 1^\circ\text{C}$). The tank was painted black, as was the platform, thus eliminating the ability of the rats to see the escape platform, the top of which was 1 cm below the water. The maze training procedure was similar to that described in earlier reports (Wyss et al. 2000). In short, animals were placed in the water and allowed to swim to locate a hidden but fixed escape platform. In our version of the water maze task, the position of the platform changes every day, such that all four possible quadrant positions for the platform locations are equally used among all groups (Lindner et al. 1992). The rat's task throughout the experiment is to find, and escape onto, the platform. Immediately following the last trial of acquisition on day 5 (i.e., trial 20), a probe trial is given. In the probe trial, the platform is removed from the pool and the animals are allowed to swim for 60 sec. Typically, a normal animal will spend most of its time searching for the platform in the quadrant where the platform was on that day.

An analysis of the results of other studies had demonstrated that rats with thalamic lesions were significantly impaired in the task after 1 wk of training but improved significantly during a second week of testing (Van Groen et al. 2000). Therefore, the group of rats with the highest pressures were tested for 2 wk. After being

tested for the first week as above, they and the control group were removed from the task for 1 wk and then retested for a second week.

Statistics

All behavioral data was analyzed by analysis of variance (SAS Institute, Cary, NC), and post hoc tests (Newman-Keuls) were carried out to determine the source of a significant main effect or interaction. As an index of the progression of learning, the first trial and the mean of trials 2 and 3 was plotted for each group across the training period, and the slope of each was calculated.

Terminal Arterial Pressures and Histology

Seven to 14 d after the end of the behavioral experiments, the rats were anesthetized with sodium pentobarbital and a PE 50 catheter was implanted into the carotid artery. The catheter was connected to a blood pressure transducer, and arterial pressures were recorded as previously reported (Wyss et al. 1999). Following a stabilization period, arterial pressure was recorded for at least 5 min, and the rats were then disconnected from the blood pressure transducer. In the rats run for 2 wk, arterial pressure was measured in both femoral and carotid arteries. Subsequent to the arterial pressure measurements, the rats were transcardially perfused with 100 mL phosphate buffered (0.1 M, pH 7.4) saline, followed by 250 mL of a 4% paraformaldehyde solution in phosphate buffer (pH 7.4). The brains were removed from the skulls and stored. The body weight (before surgery) and heart and kidney weights were measured. Following a storage period of 48 h at 4°C in a 30% sucrose solution, the brains were put on the stage of a freezing microtome and two or three 1-in-6 series of sections (30 µm thick) were cut in the frontal plane and collected in trays. One series was mounted on gelatin-coated slides immediately; this series was stained with cresyl violet and coverslipped. The second series was stained for acetylcholinesterase according to a modified method of Koelle and Friedenwald (1949), and the optional third series was stained for butyrylcholinesterase according to the method of Tago et al. (1992); this method stains the blood vessels in the rat brain. The sections were inspected by light microscopy.

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