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Brief communication

Motor and cognitive deficits in mice bred to have low or high blood pressure

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ABSTRACT

Deviations from normal blood pressure can lead to a number of physiological and behavioral complications. We tested the hypothesis that hyper- or hypotension is associated with significant differences in motor activity and coordination, anxiety levels, and spatial learning and memory in male and female mice. Compared to normotensive control mice, hypertensive mice were hyperactive and their performance was significantly worse on the rotarod (males only), cued learning (males only), spatial learning/re-learning, and spatial memory. Hypotensive mice of both genders swam more slowly and performed even worse than hypertensive mice on the rotarod, cued learning, spatial learning/re-learning, and spatial memory tasks. Across all phenotypes, females were generally more active than males in the open field and exhibited more anxiety-like behaviors in the elevated zero maze. Alterations in hemodynamics and/or neurovascular unit function may account for the observed behavioral changes in the hypo- and hypertensive mice.

1. Introduction

The human brain uses approximately 20% of the blood's entire supply of oxygen, and deviations from normal blood pressure and/or regulation of cerebral blood flow can produce differences in brain function and associated cognitive and motor deficits. For example, chronic hypertension has been associated with impairments across a number of cognitive and physical domains [1]. Additionally, the negative effects of hypertension on cognition may increase with age. A recent study showed that executive function declines more quickly in older individuals with high blood pressure than in those with normal blood pressure [2]. Chronic hypotension has also been associated with deficits in memory, attention, and processing speed [3,4]. Interestingly, deviations from normal blood pressure (either hypo- or hyper-) have been associated with increased anxiety [5], although one study showed that dialysis patients with hypotension were significantly more likely to score low on tests of anxiety [6]. In addition to the chronic behavioral effects associated with deviations from normal blood pressure, high blood pressure increases the risk of cerebral hemorrhage, and low blood pressure increases the risk of intracerebral ischemia.

One animal model of blood pressure deviation, the spontaneously hypertensive rat (SHR), is hyperactive compared to controls [7,8], although it has been pointed out that the best controls have not always been used [9]. Therefore, the SHR is often used as a model of attention deficit with hyperactivity disorder (ADHD) [9]. However, although hypertensive rats tend to be hyperactive, it is important to note that the hyperactivity may not result directly from the genetic deviations that induce the hypertension. All behaviors ultimately emerge from a host of biological and environmental factors only indirectly related to genotype [7,9–14]. Although mouse models of chronically low and high blood pressure exist, a study of the behavioral characteristics of these mice has not been published. Therefore, we tested mice bred to have low, normal, or high blood pressure on a battery of tests designed to assess a variety of behavioral domains.

2. Material and methods

All experimental procedures were performed within the regulations of the Animal Welfare Act, the National Institutes of Health Guide for the Care and Use of Laboratory Animals, "The Guiding Principles in the Care and Use of Animals" approved by the Council of the American Physiological Society, and the Animal Care and Use Committee of Loma Linda University.

2.1. Animals

Male and female spontaneously hypotensive mice (BPL/1; n = 4 males, 5 females), hypertensive mice (BPH/2; n = 3 males, 5 females), and normotensive mice (BPN/3; n = 5 males, 5 females) were obtained from Jackson Laboratories (Bar Harbor, ME). These animals were line-bred for hyper- or hypotension, modeling heritable deviations from normal blood pressure. BPH/2 mice have elevated systolic blood pressure by 5 weeks, and at 150 days differ from BPL/1 mice by 60 mm Hg. BPN/3 mice were bred as normotensive controls for the BPH/2 and

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BPL/1 strains. Thus, BPH/2 mice are hypertensive and BPL/1 hypotensive over their entire lifespan. There were no significant weight or size differences between groups. All mice were 8–12 weeks of age, and the groups were compared on a variety of behavioral tests over 8 days.

2.2. Blood pressure measurement

The tail cuff method has been shown to measure rodent blood pressure noninvasively and accurately in many studies [15,16]. We measured blood pressure weekly by determining the tail blood volume, flow, systolic and diastolic blood pressures with the heart rate simultaneously using a volume pressure recording sensor and an occlusion tail-cuff (CODA System, Kent Scientific, Torrington, CT) [17,18]. Mice were placed into an integrated animal holder prior to blood pressure management. This system involves an integrated nosecone; animals are gently restrained but the system is designed to prevent undue stress while blood pressure is being measured. This system differs significantly from the plethysmographic based tail-cuff measurement system, which measures only systolic blood pressure [19]. Before commencing our studies, blood pressures were measured during three 15-minute sessions each day for 3 days, or until we obtained stable recordings.

2.3. Behavioral tests

2.3.1. Open field activity

Activity levels were tested on days 1 and 2 by observing each animal for 30 min in open-topped opaque plastic boxes (49 cm long × 36 cm wide × 45 cm tall). Movements of each animal were recorded by an overhead camera and analyzed by a computerized tracking system (Noldus Ethovision, Leesburg, VA).

2.3.2. Rotarod

Balance and sensorimotor coordination was tested using the accelerating rotarod (Columbus Instruments, Columbus, OH) on days 1 and 3. The rotarod consists of a horizontal cylinder (7 cm diameter) divided into four 9.5 cm-wide lanes. When placed on the rotating cylinder, the mouse has to walk forward to avoid falling off. Latency to fall is the dependent variable. Two consecutive trials, in which the rotarod started at 5 RPM and accelerated by 2 RPM every 5 s, were administered per day.

2.3.3. Elevated zero maze

Anxiety-like behaviors were tested using the elevated zero maze on days 2 and 3. The zero maze (CNC Router Guy, St. Louis, MO) is a 100 cm outer-diameter, 10 cm wide plastic track in the shape of a circle and elevated 100 cm above the floor. Half of the track (2 opposing quarters) is brightly lit and has open sides. Walls (30 cm tall) enclose the other 2 opposing quarters, which are much dimmer. Each mouse was placed in the center of an open track quarter and observed for 5 min. Time spent in the open versus closed quadrants of the track was recorded.

2.3.4. Water maze

General associative learning and spatial learning and memory were tested using the water maze, a metal pool (110 cm in diameter) filled with water made opaque using non-toxic tempera paint. The animal's task is to find and climb onto an escape platform (11 cm in diameter), the surface of which is either 1.5 cm above the water's surface (cued task), or submerged 1.5 cm below the water's surface (spatial task). Each animal was administered 10 trials (60 s max) per day in 5 blocks of 2 consecutive trials. The animal was manually guided to platform after 60 s, where it was allowed to rest and observe its surroundings for 10 s, at which point the next trial began. Swim distance, escape latency, and cumulative distance to the platform are the dependent variables captured by the overhead camera and computerized tracking system (Noldus Ethovision).

2.3.4.1. Cued water maze. Cued (visible platform) learning was tested on day 4. After every 2 trials, the platform was moved to a new location. Mice were always released nose against the wall opposite the platform location.

2.3.4.2. Spatial water maze. Spatial (hidden platform) learning and memory were tested on days 5–8. For this task, the submerged platform remained in the same location for all 10 trials of each day. Mice were released nose against the wall from 1 of 4 locations around the tank in a semi-random and counterbalanced design. The inter-block interval was approximately 45 min. Day 6 began with a probe trial, in which the platform was removed and mice were allowed to swim freely for 60 s. Time spent in day 5's platform quadrant and number of entries into the former platform location were assessed. Following the probe trial, the platform was placed into the maze in a new location and spatial testing resumed. Day 7 was similar, with a new platform location, and day 8 consisted of a probe trial to assess the spatial memory of day 7's platform location.

2.4. Statistical analysis

An α-level of .05 was used for all statistical significance tests. Main and interaction effects were analyzed using mixed-model repeated-measures ANOVAs and Scheffe *post-hoc* tests.

3. Results

3.1. Blood pressure

At 13 weeks of age, male and female normotensive (BPN/3) mice had mean blood pressures of 118 ± 10 and 126 ± 9 mm Hg, respectively. Male and female hypotensive (BPL/1) mice had mean blood pressures of 90 ± 6 and 100 ± 5 mm Hg, respectively, and male and female hypertensive (BPH/3) mice had mean blood pressures of 145 ± 6 and 152 ± 4 mm Hg, respectively (Fig. 1).

3.2. Behavioral tests

3.2.1. Open field activity

Hypertensive mice of both sexes were significantly more active than hypo- or normotensive mice, which did not differ ($F(2, 24) = 17.7$, $p < 0.00003$; Fig. 2). A significant gender × time × phenotype interaction revealed that hypo- and hypertensive females started out more active than males for ~10 min before settling down to male levels of activity, whereas normotensive females stayed more active than males over the course of the 30 minute test ($F(18, 189) = 2.6$, $p < 0.0009$).

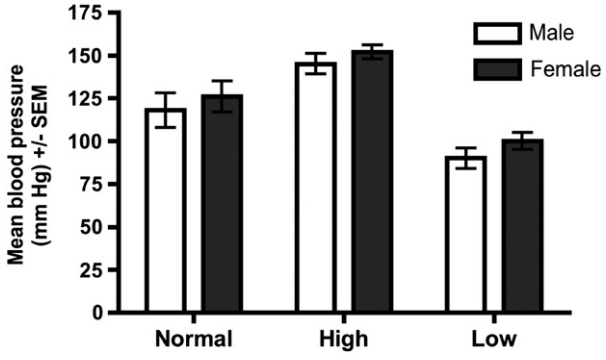

Fig. 1. Blood pressure. Bar graph showing the blood pressure recorded by non-invasive tail-cuff method in male and female from three groups of mice.