Peculiarities of Active Avoidance Conditioning in Rats with Various Forms of Inherited Arterial Hypertension

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Peculiarities of active avoidance conditioning were studied in NISAG rats (hereditary stress-induced arterial hypertension) and spontaneously hypertensive SHR rats. Conditioning was successful in 90% normotensive Wistar rats and in only 9.1% NISAG rats. Hypertensive SHR rats were intermediate between Wistar and NISAG rats by their learning capacity (66.7%). Our results suggest that differences in learning capacity of hypertensive rats are determined by genetic characteristics of animal behavior and emotional state, rather than blood pressure elevation.

Key Words: *arterial hypertension; memory; conditioned active avoidance response*

Hypertension can result in the impairment of such important brain function as memory [4,6,10]. Published data show that hypotensive therapy has no effect on the development of dementias or memory improvement [3,12]. Therefore, memory disorders do not depend on hypertension. Studies on biological models of genetic and induced hypertension did not elucidate the role of hypertension. Spontaneously hypertensive SHR rats serve as a model of genetic hypertension. These animals have specific characteristics of behavior and cognitive function, which reproduces attention deficiency syndrome in hyperactive children [9]. SHR rats are characterized by neuronal and neurotransmitter changes in brain structures playing a role in emotional and cognitive function [6-8,13,14]. These specific features make difficult evaluation of hypertension/memory cause-effect relations. Therefore, another model of hypertension with other behavioral and emotional characteristics is of particular interest in this respect. Comparative studies of memory processes in 2 strains of animals should be performed. NISAG rats were selected from outbred Wistar rats and serve as a model of inherited stress-induced arterial hypertension [2]. By the characteristics of unconditioned behavior, NISAG rats differ from SHR rats by hyperreactivity of behavioral parameters, blood pressure, and corticosterone level to novelty. As distinct from SHR rats, NISAG rats do not exhibit hyperactivity and low anxiety [1,2[.

Here we compared the acquisition of conditioned active avoidance response (CPAR) in hypertensive NISAG and SHR rats.

MATERIALS AND METHODS

Experiments were performed on male rats of 3 genetic strains aging 5 months. SHR (n=9), NISAG (n=11), and Wistar rats (n=10) were obtained from the Laboratory of Animal Breeding (Institute of Cytology and Genetics). The animals were maintained in plastic cages (2 rats per cage) under standard conditions. They were adapted to novel environment for 10-12 days before the start of the study. CPAR training was performed in a shuttle box (IFT-04 software). The animals were familiarized with the device for 3 min before learning. An electric lamp (10 W) built in the anterior wall of the

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chamber above the door was turned on in the rat compartment. Electric current (0.7 mA) was delivered through the metal grid floor 5 sec after presentation of the conditioned stimulus. Electric current and light were turned off when the rat moved to another compartment. The time interval between conditioned and unconditioned stimuli randomly varied from 22-30 sec. The rats were trained for 2 days. Each session consisted of 50 trials. The latency of stimulus-induced transition, the number of combinations until the appearance of the 1st correct response, number of combinations until CPAR retention (7 consecutive correct responses), and number of interstimulus transitions were recorded.

The significance of intergroup and intragroup differences was evaluated using one-way and two-way ANOVA (Statgraphics software).

RESULTS

CPAR performance in Wistar, SHR, and NISAG rats reached 90, 66.7, and 9.1%, respectively.

The lowest number of combinations until the appearance of the 1st correct response was noted in Wistar rats (Fig. 1, *a*). Highly significant differences were revealed between Wistar and NISAG rats ($F_{2,19}$=16.32, p<0.001). This parameter in SHR rats was higher than in NISAG rats ($F_{2,18}$=9.90, p<0.01). The animals significantly differed by the number of presented combinations until the appearance of 7 correct responses (Fig. 1, *b*). Four of ten Wistar rats exhibited this reaction after the 27th trial in session 1 (27.0±5.6). Other Wistar rats learned the response after the 58th trial in session 2 (58.8±2.5). Three of 9 SHR rats were trained after the 41st trial in session 1 (41.6±0.6). Three SHR rats learned the response after the 86th trial in session 2 (86.6±5.3). Significant differences were found between these groups of animals ($F_{2,17}$=7.12, p<0.05). ANOVA showed that NISAG rats significantly differed from Wistar rats ($F_{2,19}$=25.56, p<0.001) and SHR rats ($F_{2,18}$=4.78, p<0.05). These differences were associated with poor learning capacity of NISAG rats in both sessions. Only one NISAG rat demonstrated the required number of conditioned responses after 68 trials. By the number of interstimulus transitions, NISAG rats demonstrated lowest activity compared to animals of other groups (Fig. 1, *c*). However, ANOVA revealed statistically significant differences only between NISAG rats and control Wistar rats ($F_{2,19}$=10.34, p<0.003). This parameter also differed in SHR and Wistar rats ($F_{2,17}$= 4.32, p<0.05).

The mean latency of transition was determined for 5 consecutive blocks of session 1 (10 combinations in each block). Factors of group ($F_{2,27}$=14.24, p<0.001) and time ($F_{4,108}$=11.76, p<0.001) were significant. Until the end of session 1, the latency of transition in NISAG rats significantly differed from those in Wistar and SHR rats (p<0.001, Fig. 2). No differences were found between Wistar and SHR rats. Each group of animals exhibited the specific type of changes. Study of intragroup differences showed that NISAG rats with a long delay of CPAR are characterized by a sharp decrease in transition latency in the 4th block ($F_{1,27}$=11.28, p<0.002 compared to the 1st block). Low basal value of transition latency for SHR rats remained unchanged from the 1st to the last block in session. Transition latency for control Wistar rats progressively decreased, which resulted in the appearance of significant intragroup differences between the 1st and 3rd blocks of combinations ($F_{1,27}$=5.00, p=0.03).

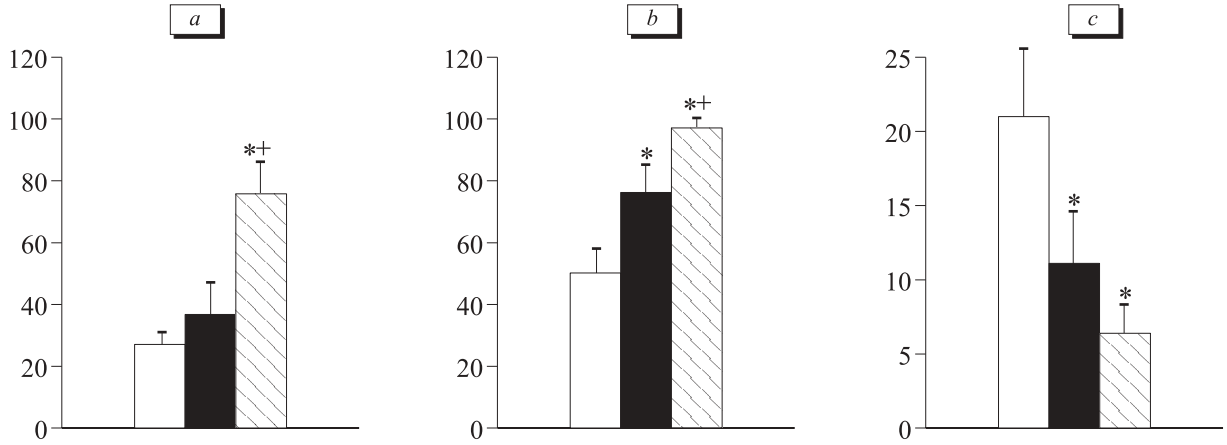

Fig. 1. CPAR learning in hypertensive and normotensive rats. Number of combinations of conditioned and unconditioned stimuli until the appearance of the 1st correct response (*a*); number of combinations until CPAR retention (*b*); number of intersignal transitions (*c*). Light bars, Wistar rats; dark bars, SHR rats; shaded bard, NISAG rats. *p<0.05 compared to Wistar rats; +p<0.05 compared to SHR rats.

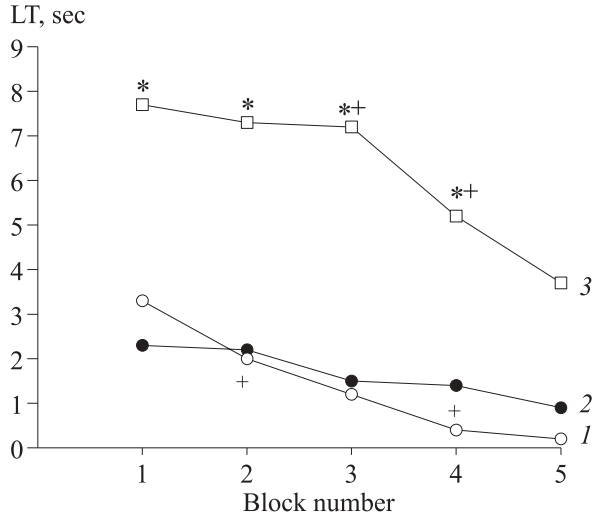

Fig. 2. Transition latency after nociceptive stimulation during learning in session 1: Wistar (*1*), SHR (*2*), and NISAG (*3*). **p*<0.01 compared to Wistar and SHR rats; +*p*<0.05 for intragroup differences between the 1st and subsequent blocks.

The long delay of CPAR in NISAG rats probably prevented the achievement of learning criterion. This specific feature can result from the effect of stress and high alertness of animals under conditions of repeated aversive stimulation, which is augmented by genetically determined hyperreactivity of NISAG rats [2]. The behavioral response of NISAG rats to nociceptive stimulation differs from that of Wistar and SHR. These differences are manifested in passiveness and freezing of NISAG rats in the dangerous compartment. Previous studies confirmed the existence of phenotypic relationships between behavioral parameters in the CPAR task [5]. Highly significant negative correlations were revealed between transition latency and number of CPAR, as well as between transition latency and number of interstimulus transitions. Our results are consistent with these data. Learning ability of hypertensive rats was lower than in normotensive control animals. However, learning ability differs in NISAG and SHR rats exhibiting various behavioral and emotional characteristics. Therefore, learning deficit in NISAG rats is associated with not only negative effect of hypertension. Further investigations should be performed to evaluate associative capacities of these rats.

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