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COMPARATIVE CHARACTERISTICS OF HIPPOCAMPUS-DEPENDENT BEHAVIOR IN HYPOKINESIA AND AGING

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Abstract

Hypokinesia is a widespread risk factor for the pathogenesis in a variety of organ-systems, particularly for disorders of the central nervous system. For the aging population hypokinesia is frequently the main life-style; hypokinesis by the interruption of self-motion, restriction of spatial and head direction provide a type of cognitive paralysis. We have investigated learning of spatial form radial maze in 7, 15 and 45 days repeated hypokinesia/hypodynamic conditioned rats. Five groups involved 40 young rats aged 5-6 months (body weight=160-180 *g*) and 10 adult rats aged 18-22 months (body weight 180-250 *g*). Animals were divided into 7-, 15-, and 45-day hypokinetic groups, exposed to hypokinesia 22 hours per day in narrow individual Plexiglas cages, which restricted their movements in all directions. There were also control and aged-control groups. Controls and adult rats remained undisturbed during the period of stress. Rats were tested in elevated plus maze (EPM) and Y-maze before and after hypokinesia exposure. After 7, 15 and 45 days of hypokinesia rats were trained on the spatial form of radial arm maze. Reference (RM) and working memory (WM) errors were calculated. In 15-day hypokinetic rats, the lowest level of WM errors was registered, whereas in adult rats it was the highest. The relative improvement of RM in 15-day hypokinetic group was noticed compared with control ($P < 0.047$). The continuous spatial alternation severely declined in 7 days of hypokinesia ($P < 0.001$). The EPM test revealed that short-term hypokinesia was provided by avoidance and lasting hypokinesia correlated with exploratory tendencies. Based on these findings, we consider that hippocampal-dependent allocentric spatial memory improvement is evident in 45-day hypokinetic group, while the egocentric response attitude is setting in lasting hypokinesia. We emphasize the contribution of hypokinesia to hippocampus mediated relational contextual memory among multidimensional memories.

Keywords: hypokinesia, radial maze, working and reference memory, memory system.

Introduction:

The human life in the modern society is characterized by the impact of various risk factors, among which hypokinesia (HK) and aging are of no less significance. Especially in present-day society, the role of HK has increased due to possibilities of on-site information access, automated production processes, implementation of high technologies in working conditions, and transportation. On the other hand, demographic data of the modern society declare an increase of aged population and decline of individuals with working capacity. Studies on the impact of hypokinetic and aging factors in cognitive sphere are valued in view of supporting the working capacity and benefit of treatment and prevention [*Fordyce D., Farrar R., 1991*].

Both HK and aging are widespread risk factors for the pathogenesis of a variety of organ-

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systems, particularly for disorders of higher nervous activity [*Akopian V. et al., 1993; Akopian V., 1999; Edgerton V., Roy R. 1996; Langlet C. et al., 2001*]. Summarizing the above-mentioned aspects, it becomes significant to comparatively evaluate the influence of HK and aging on the behavioral-cognitive emotional sphere. Therefore, for ensuring life quality and healthy life style it is important to describe the pathogenetic role of aging and HK interaction, as well as mechanisms of socio-biological adaptation.

Despite the extensive research devoted to interaction between various memory systems [*Mair G., 2002; Poldrack A., Packard G., 2003; Woodson C. et al., 2003; White M., 2004*], there are still contradictory suggestions about their involvement in different behavioral activities.

The association of stimuli, their relational, contextual, and temporal organization are supposed to be regulated by the hippocampal dependent system [*Kesner R., 1998; Eichenbaum H., 1999; Dudchenko A. et al., 2000; Knierim J., McNaughton L., 2001; Poldrack A., Packard G., 2003*]. There are also parallel processing memory systems such as dorsal striatum-dependent and amygdal-mediated systems [*Packard G. et al., 1994; McIntyre K. et al., 2002; Kesner R., Rogers L., 2004*]. Particularly, the solution of radial arm maze [*Olton D. et al., 1979*] reflected activation and interactions between all the above-mentioned memory systems [*Chai S.-C., White M., 2004;Loren M., 2004; Mizumori S. et al., 2004*]. Moreover, there are vast amounts of clinical, experimental, and computational analyses of multiple dissociations and cooperation between the declarative, procedural and emotional memory systems [*Jarrard L., 1983*]. Thus, in mentally impaired experimental animals the studies reveal hippocamp, striatum and amygdala dependent strategies in radial arm maze as well as managing various types of information about them.

Declination of cognition along with the HK [*Navasardyan G., Yeritsyan N., 2003; Yeritsyan N., 2005*] and aging [*Brennan A. et al., 2007*] was reported by different authors. Summarizing the above mentioned aspects it becomes significant to comparatively evaluate the action of HK and aging with the cognitive emotion sphere. Thus, our aim was to study the difference between "natural" (aging- related) and experimentally induced HK.

In the current study we investigated the comparative data of some hipocamp-dependent behavioral parameters in young hypokinetic and aged rats. Specificity of working and reference memory, spatial recognition changes were observed in all experimental groups. Data obtained can provide the grounds for appropriate choice of medical and paramedical interventions aimed at correction of cognitive disorders.

Materials and Methods:

Animals: Forty rats aged approximately 5-6 months and ten 16-18 months old inbred rats (b.w. = 180-250 *g*) tested on Y-maze homogeneity were randomly divided into four groups. Three groups of rats were exposed to repeated HK 22 hours per day for 7, 15 and 45 days, accordingly. HK was modeled by exposure of rats in narrow individual cages, which restricted the movement of rats in all directions. Two hours per day hypokinetic rats were replaced into their homecages, where they could easily move and contact with each other. Control and adult groups remained in the unrestricted state.

The experiments were done in accordance with the European Communities Council Directive (86/609/EEC) for the care and use of animals for experimental procedures. The "Protocol" was approved by the Animal Care and Ethics Committee of the Yerevan State Medical University. All efforts were made to minimize animal suffering and to reduce the number of animals used.

Apparatus

Radial Arm Maze: The maze consists of eight arms with a 45º angle between adjacent arms extending from the central platform (diameter=25 *cm*), surrounded by 10 *cm* height Plexiglas walls. The floor of arms and central platform were painted black. The radial arm maze was placed in the center of the curtained enclosure. The four poster sheets and four suspended objects were placed over the black curtain and extended upon each baited arm. Plastic food cups were placed on the floor at the end of each radial arm. The rats could easily take food from the cup while standing on the arm or on the floor next to the arm. The positions of the baited arms were fixed throughout the training trails (fixed position of reward task; FPRT).

Y-maze: The maze was made of black painted wood; each arm was 30 *cm* long, 12 *cm* wide and 10 *cm* high. The floor of each arm was cleaned with 70% ethanol before trials. The floor of each arm was covered by paper, which was changed between trials. Each rat was placed at the centre of maze and allowed to move freely through the maze during an 8-*min* session. The series of arm entries, including returns into the same arm, were tape recorded [*Lalonde R., 2002*].

Elevated Plus Maze. The elevated plus maze consists of two open arms (27 x 5 x 0.25 *cm*) and two closed arms (27 x 5 x 15 *cm*) extended from a common central platform (15 x 5 *cm*). The apparatus was made in Plexiglas (black floor, clean walls) and elevated to a height of 40 *cm* above floor level. Open-arm exploration was encouraged by the inclusion of a slightly raised edge (0.25 *cm)* around their perimeter and by testing under indirect dim white light. All tests were conducted between 10 a.m. and 7 p.m.

Procedure

Training: After HK rats were trained on spatial form of 8 arm radial maze during five days, four trials per day. Training task was organized as fixed position of reward task. Four arms from eight (Nos. 1, 2, 4 and 7) were baited with chocolate food pellets for each daily training trial. Training consisted of 10 *min* trial or 16 entries of arms with 5 *min* intertrial periods. During intertrial periods rats were placed into their homecages, which were in the same experimental room apart from the maze's tent. After solution of maze, rats remained in the maze for the voluntary unreinforced exploration until 10 *min* elapsed or 16 entries were made. Before each training trial the maze was rotated to the left by one arm (45°) and was cleaned with 70% ethanol, so that during maze solution rats could not use any non-spatial cue. Rats had to rely mostly on spatial cues.

Working memory (WM) errors (re-entry into the prior visited baited arm before task solution), reference memory (RM) errors (entry into the unbaited arm before solution) and working reference memory (WRM) errors (reentry into the unbaited arm before task solution) were accounted. For defining the strategy of maze solution the angles of arm entry (45º, 90º, 135º, 180º and 360º) were also accounted [*Smith C. et al., 2004*].

Y-maze testing was performed before and after hypokinetic exposure. Rats were exposed to alternation behavior test during eight minutes. An alternation was defined as entries into all three arms on consecutive occasions. The number of maximum alternations was calculated as the total number of arm entries minus two, and the percentage of alternations was taken as follows:

$$\frac{\textit{actual alternations}}{\textit{maximum alternations}} \times 100.$$

EPM is testing before and after exposure to HK. The number of open and closed arm entries, time spent in closed, open arms and hub were calculated.

Statistical analyses: Significant interactions were followed up by one-way ANOVA of the group factor at each level of the repeated-measures factor. Student's *t*-test for independent samples and non-parametric tests was used. All analyses were done by SPSS statistical software package. Statistical significance was assigned by P<0.05.

Results

Radial arm maze: The differences of working memory (WM) and reference memory (RM) errors between groups are shown in Figure 1. A one-way ANOVA revealed significant group effects on the means of reference memory errors (F = 1.96, P <0.1), working memory errors (F = 6.517, P <0.001) and working reference memory errors (F = 2.09, P <0.083) (Figure 1). Tukey's post hoc test showed significant reference memory error difference between control and 15-day hypokinetic groups (P < 0.047). Significant working memory error difference between control and 15-day hypokinetic groups were also revealed (P < 0.007). Post hoc test also showed significantly more working memory errors than 7-day hypokinetic (P <0.028) and 15-day hypokinetic groups (P < 0.001) (Figure 1).

There was a significant decrease of 90 degree of arm entry between the second and third day of maze training in rats of 7-day hypokinetic group (t = 2.2, P < 0.034, 2-tailed) (Figure 1).

Y-maze: The continuous spatial alternation behavior was tested in spatial form of Y-maze. A one-way ANOVA revealed significant group effected on the means of spatial alternation behavior (F = 3.115, P < 0.022). Post hoc Dunnett's C test showed significant declination of spatial alternation behavior in 7-day hypokinetic rats compared with the control group (P < 0.007) and 45-day hypokinetic rats (P < 0.001) (Figure. 2).

Elevated plus maze: ANOVA test reveals non-significant group effects for open arm time (F = 3.026, P < 0.061) and close arm time (F = 2.713, P < 0.08) accounted by control, 7- and 15-day hypokinetic groups. Student's test revealed a significant difference between the mentioned and 45-day hypokinetic groups (P < 0.05). Adult rats group is not differentiated from 45-day hypokinetic rats.

Discussion:

Radial arm maze; The experimental HK does not damage rat's learning ability to solve a radial arm maze. The result from this study revealed reference memory differences between experimental and control groups throughout the serial learning procedure. Particularly, a significant improvement of reference memory in 15-day hypokinetic rats group takes place compared with other groups. The 15-day hypokinetic group improves the reference memory on the third day of learning: earlier than others.

On the other hand, working memory of 7- and 15-day HK rats was better than in control, adult and 45-day hypokinetic rats groups. Declination of reference and working memory of adult rats group was especially apparent compared with other experimental groups. This was also approved by other researchers [*Brennan A. et al., 2007*].

The stability of learning along the whole period of HK reflects evolutionary developed reliable memory systems of brain, which are able to perform parallel information processing [*Phillips R., LeDoux J., 1992; Devan D., White M., 1999; Nikol K. et al., 2007*].

The trial and session analyses of learning of rats show the dynamic interaction and assistance of memory systems [*Devan D., White M., 1999*;

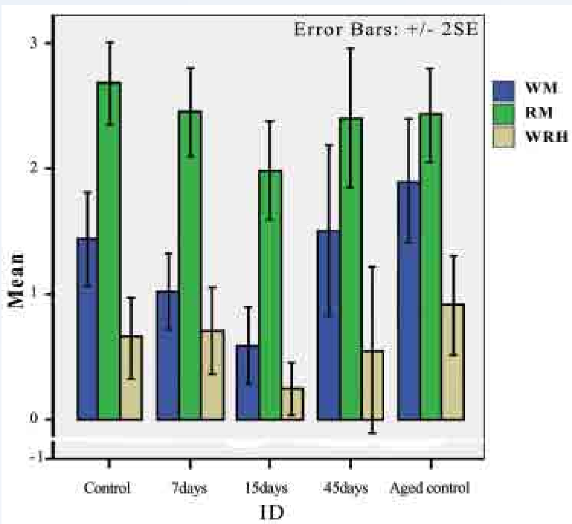

Figure 1. *Reference, working, and working reference memory errors in experimental groups.*

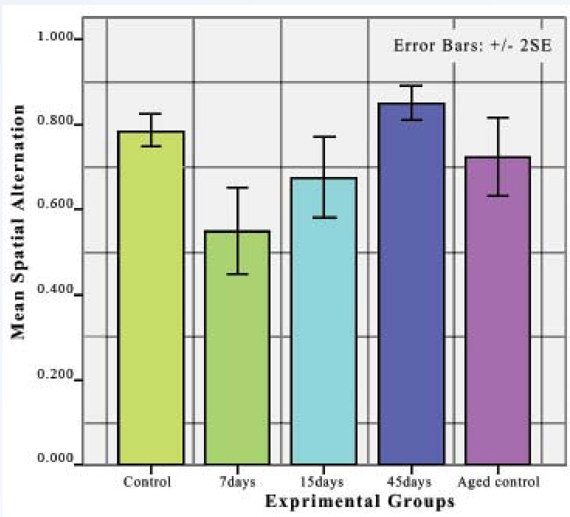

Figure 2. *Spatial alternation behavior in the Y-maze.*

Yeshenko O., Mizumori S. et al., 2007]. The behavioral expression of "learned maze" provides cooperative and/or competitive interaction of all components [*Devan D., White M., 1999*; *Compton M., 2004*].

The strategy used by rats to solve radial arm maze provides the sequence of involvement of locomotor search approach and various memory systems [*Hoffman M. et al., 1999*]. The locomotor approach provides type of context for spatial learning. The adjusted arm (45° arm entries) was chosen for 45-day hypokinetic rats. This locomotor approach reflected the response habit formation and egocentric strategy [*Bustos M. et al., 2003; White M., 2004; De Leonibus E., 2005*]. For the 7-day hypokinetic group by obtuse angles of arm entries allocentric random arm choosing is assumptive [*Bustos M. et al., 2003; Kennedy J., Shapiro L., 2004; De Leonibus E. et al., 2005; Smith M., Mizumori J., 2006*].

Y-maze: The results indicate to difference for the continuous spatial alternation behavior in Y-maze between experimental groups. The significant increment of spatial alternation behavior in 15-day hypokinetic group compared with 7-day hypokinetic group is mentioned. Despite a declination of spatial alternation behavior after the short-term of HK, after 15 days of HK it progressively improved.

Despite the low level of spatial alternation behavior in adult rats group compared with the control group this is higher than in 7- and 15-day HK groups. Only in 45 days the spatial alternation behavior improved compared with adult rats group.

The spatial disorientation is responsible for the failed continuous spatial alternation. The association of egocentric motor information with allocentric spatial information is more comprehensive for continuous alternation behavior in Y-maze [*Douglas R., 1966; Olton D. et al., 1979; Dudchenko A., 2004; Holscher C. et al., 2004; Hughes N., 2004; Smith M., Mizumori J., 2006*].

The increase of sequential arm entries for 15-day hypokinetic rats could be caused by disrupt of one of the informational cooperation [*Phillips R., LeDoux J., 1992; Packard G. et al., 1994; Poldrack A., Packard G., 2003*]. The disrupt of egocentric motor strategy for control and 7-day and the allocentric spatial one for 45-day hypokinetic and adult rats are suggested.

Elevated plus maze: We found that in 7-day hypokinetic group the avoidance and fear conditioning increased, while in the 45-day hypokinetic group the exploratory approach reaction was privileged.

It is generally accepted that amygdala is responsible for aversive, fear conditioning, freezing, and avoidance reactions [*Maurice T. et al., 1994; McIntyre K. et al., 2002*]. Concurrently, studies described the absence of differential-outcomes effect in amygdala impaired rats for discrimination learning and to sensory aspects of reward representation [*LeDoux J., 2000; Yeshenko O., Mizumori J., 2007*]. With the decreased amygdala activity hedonic evaluation, the palatability of reinforce is changed [*Balleine B., 2000; Mizumori S. et al., 2004*].

Due to comparable activation of amygdala response in 7-day hypokinetic group revealed by EPM behavior it was possible to partially explain better learning of radial maze. Parallel processing of hippocampal and amygdala mediating memory systems are suggested.

Conclusion

In our experimental apparatus all efforts were done to reduce intramaze and enriched extramaze cues. In these place tasks usage of allocentric win-stay foraging strategy could be the successful one. Although, 7- and 45-day hypokinetic rats revealed win-shift foraging strategy compared with control group as it was apparent by declination of working memory errors.

In the adult rats group declination of working and reference memory was revealed. The working memory of 45-day hypokinetic and adult rats was the same. But spatial recognition of 45-day hypokinetic rats was higher than in adult rats group.

On the other hand, one possibility is that due to utilization of spatial allocentric information with shifting strategies 7-day hypokinetic rats improve reference memory faster than 45-day hypokinetic rats. We suggest that lasting HK promotes the egocentric strategy. This fact was proved by data from angles of entries in radial maze and spatial alternation behavior in Y-maze.

The improvement of reference memory and declination of working memory were assigned in aged rats compared with the control group. There was no difference of working memory between aged and 45-day hypokinetic groups, but the spatial recognition of 45-day hypokinetic rats was better than in aged rats.

After solution of the radial maze rats remained in the maze for the voluntary unreinforced exploration exhibited by amygdala system [*Blundell P. et al., 2001; 2003*]. In this case we are suggesting the phenomenon of latent learning for spatiality. Probably, 7-day hypokinetic rats acquire the spatial information specific for maze environment more effectively, which was revealed by EPM data.

The possible explanation is cooperation between hippocampal-amygdala systems for 7-day hypokinetic groups and hippocampal-striatum system for 45-day hypokinetic group.

There are similar tendencies in certain features of cognitive behavioral reactions between long term HK and aging. In summary, we concluded on dynamic interaction and flexibility of memory systems and locomotor strategies in various natural conditions, particularly in hypokinetic condition.

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