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Effects of beta-adrenergic antagonist, propranolol on spatial memory and exploratory behavior in mice

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ABSTRACT

The beta-adrenergic system has been suggested to be involved in novelty detection and memory modulation. The present study aimed to investigate the role of beta-adrenergic receptors on novelty-based spatial recognition memory and exploratory behavior in mice using Y-maze test and open-field respectively. Mice were injected with three doses of beta-adrenergic receptor antagonist, propranolol (2, 10 and 20 mg/kg) or saline at three different time points (15 min prior to training, immediately after training and 15 min before test). The results showed that higher doses of propranolol (10 and 20 mg/kg) given before the training trial impaired spatial recognition memory while those injected at other two time points did not. A detailed analysis of exploratory behavior in open-field showed that lower dose (2 mg/kg) of propranolol reduced exploratory behavior of mice. Our findings indicate that higher dose of propranolol can impair acquisition of spatial information in the Y-maze without altering locomotion, suggesting that the beta-adrenergic system may be involved in modulating memory processes at the time of learning.

1. Introduction

Noradrenergic innervation in the central nervous system (CNS) is widespread. As one of the most important neural modulators in the brain, norepinephrine (NE) is involved in the regulation of many brain functions, including the wake/sleep cycle [1], memory modulation [13], synaptic/cortical plasticity [23], and pain modulation [26]. The primary source of NE in the mammalian forebrain is found in nerve terminals emanating from cell bodies located in the brainstem nucleus, the locus coeruleus (LC). Furthermore, LC is the sole source of NE in the hippocampus and the neocortex, regions critical for higher cognitive and affective processes [1,12].

Studies using adrenergic receptor agonists and antagonists have provided a considerable amount of evidence for the notion of adrenergic involvement (especially the beta-adrenergic system) in memory processing. Activation of β-adrenergic receptors with agonists enhances memory retention in either neonatal or adult rats [11,34]. Conversely, administration of a beta-adrenergic antagonist impairs memory for inhibitory avoidance [25], odor-reward association [29], and the water maze in animals [4,16] and also memory for an emotionally or physically induced arousal in humans [3].

Novelty exploration is accompanied by increased hippocampal noradrenergic activity, driven by enhanced firing of the LC in the brain [19,37,28]. The hippocampus may act as a novelty detector, conducting mismatch predictions by comparing stored information with new incoming cues [20]. Activation of β-adrenergic receptors can induce long-term potentiation (LTP)-like phenomena in the dentate gyrus (DG) [7,6] and the blockade of β-adrenergic receptors blocks distinct types of late-LTP in the DG of freely moving animals [31]. Moreover, activation of β-adrenergic receptors has been shown to enhance memory formation and LTP maintenance [15,32]. This evidence suggests that the β-adrenergic system may involve in novelty dependent memory modulation and exploratory behavior.

The Y-maze is a two-trial spatial memory task based on the innate tendency of rodents to explore novel environments that minimizes emotional activation. This kind of memory is also sensitive to hippocampal damage (CA3, CA4 or DG) [5]. The present study aimed to investigate the involvement of β-receptors in acquisition, consolidation and retrieval of spatial memory and compare different effects of propranolol administration on novelty exploratory behavior in Y-maze and open-field. Our hypothesis was that by systemic administration, propranolol, a lipophilic β-blocker that crosses the blood–brain barrier easily, may interfere with spatial memory processing in mice with a less emotional state.

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2. Material and methods

Male ICR mice (22–26 g body weight, 8 weeks of age) were obtained from a breeding colony at the Kunming Medical College (Kunming, PR China). When arriving, they were housed in groups of 8 per cage under standard conditions (12-h light/dark cycle with lights on from 07:00 to 19:00 h). Mice were freely feeding and familiarized with the experimenter for 1 week prior to experiments. Experiments were conducted in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals and approved by the Institute.

DL-propranolol (Sigma, St. Louis, USA) were diluted in concentrations of 2.5, 1.25 and 0.25 mg/ml with sterile saline that was also used as vehicle. Drugs were administered intraperitoneally to each mouse in an injection volume of 8 ml/kg.

Two Y-mazes, made of gray polyvinylene, were placed in a quiet, illuminated room. Each maze consisted of three arms ($8 \times 30 \times 15$ cm, width × length × height), with an angle of 120° between each arm. The three identical arms were randomly designated: 'Start' arm, in which the mouse began to explore (always open); 'Novel' arm, which was closed off during the first trial, but open in the second trial; and 'Other' arm (always open). The maze floors were covered with sawdust, which was mixed after each trial in order to eliminate olfactory stimuli. Visual cues were placed on the walls of the arms.

The Y-maze test consisted of two trials separated by an intertrial interval (ITI) to assess spatial recognition memory. The first trial lasted 5 min (acquisition trial) and allowed the mouse to explore only two arms (start and other arms) of the maze, with the third arm (novel arm) blocked off. The start, novel, and other arms were randomized between mice to reduce arm bias effects. After 1 h ITI, the second trial was conducted, during which all three arms were accessible; the mouse was returned to the same starting arm and allowed to explore all three arms for 5 min (recall trial). Entry was defined as the entry of all four paws into one arm. Through a ceiling-mounted CCD camera, all trials were recorded on a VCR. Video recordings were later analyzed so that the number of entries and time spent in each arm during the recall trial could be determined. The effects of novelty and familiarity were analyzed by comparing these measures in all three arms.

Since the Y-maze can be assessed several times in the same animal [10], mice were therefore tested three times with different injection time. A total of 40 mice were used and arbitrarily placed in one of four treatment groups: injected with either saline (control) or propranolol at doses of 2, 10 or 20 mg/kg (abbreviated as: P2, P10 and P20; $N = 10$ per group). The drugs were injected at one of the following three time points in turn: 15 min prior to the first Y-maze trial (Pre), immediately after the first Y-maze trial (Imm) or 15 min prior to the second Y-maze trial (Post). The interval between sessions was 1 week. Experiments were performed in a split-plot design. The drug doses and the time of injection were chosen according to the pharmacokinetic characteristic of propranolol reported by previous study [2] and our pilot data.

The open-field apparatus (600 mm × 600 mm × 500 mm) was a white Plexiglas box with a black floor divided into 16 squares. Four squares were defined as the center and the 12 squares along the walls as the periphery. Each mouse was gently placed in the very center of the box and behavior was recorded by a video camera for 5 min during the first exposure to the open-field apparatus. The apparatus was cleaned with 70% ethanol after each trial. The number of rearing, grooming, defecation and the number of times mice entering the central four squares (central field penetration) were manually scored by a researcher blinded to the experimental manipulations. Rears were scored when a mouse raised both front paws from the floor and leaned its front paws against a wall. Time spent in the central four squares began when mice placed all four paws in it and ended when mice completely left the region (i.e. all four paws out). Horizontal distance (horizontal locomotion/m) walked in the open-field and the time spent in central four squares (inside square/s) were analyzed automatically using software developed by our lab.

The mice were arbitrarily placed in one of four treatment groups: saline, P2, P10 and P20 (saline, P20: $N = 12$; P2, P10: $N = 13$). Each mouse was removed from its cage, gently weighed, injected intraperitoneally15 min before the test.

Data were expressed as: (1) duration of arm visits in the 5-min-recall trial (with novel arm duration being a measure of spatial recognition memory); and (2) the total number of visits to each arm in the 5-min-recall trial. Data were expressed as mean ± standard error of the mean (SEM) and analyzed using the SPSS statistical software package (Version 10).

Differences between groups for time spent in the different arms, and for total number of arm visits were assessed using two-way analysis of variance (ANOVA) with repeated measures where appropriate. Time of injection (Pre, Imm, Post) and Treatment (saline, propranolol) were considered between-group factors, whereas arm (novel, start, other) was considered a within-group factor. One-way ANOVA was used for further analysis of the difference between groups in the novel arm and in the open- field parameters. Finally, post-hoc, between-group comparisons were completed with Fisher's Least-Significant-Difference test (LSD). Differences between groups were considered significant if $p < 0.05$.

3. Results

Animals did not exhibit any sign of stress or excessive discomfort during or after injections of drugs. We first analyzed the duration and number of arm visits (data not shown) using univariate analysis during the acquisition trail, there was no significant difference in the duration and entry between those groups, showing the basic exploration behaviors and locomotion during the first trial was similar.

The analysis of duration of arm visits revealed a main effect of treatment. The P10 and P20 groups spent less time in the arms, as opposed to the center of the maze, when compared to the mice in the control group (effect of group: $F_{(3,108)} = 3.11$, $p < 0.05$; LSD: control vs. P10, $p < 0.01$; control vs. P20, $p = 0.05$). All mice spent less time visiting arms on the recall trial when they were injected at Post than at Pre or Imm (effect of time: $F_{(2,108)} = 12.53$, $p < 0.01$; LSD: Post vs. Pre, $p < 0.01$, Post vs. Imm, $p < 0.01$)

The repeated variable of arm was significant and interacted significantly with treatment ($F_{(6,108)} = 2.80$, $p < 0.05$), and both treatment and time (third-order interaction, $F_{(12,108)} = 1.80$, $p = 0.05$). A posteriori analysis breaking this interaction by time revealed that mice injected at Imm or Post spent more time in the novel arm, regardless of which group they belong to (significant main effect of arm at Imm and Post, Imm, $F_{(2,36)} = 17.73$, $p < 0.01$; Post, $F_{(2,36)} = 14.64$, $p < 0.01$, with no significant interaction between arm and group; see Fig. 1). A different pattern of results was noted for the mice injected at Pre. The mice in P10 and P20 groups did not spend more time in any given arms. However, mice in control and P2 groups spent more time in the novel arm compare to other arms (significant arm by group interaction, $F_{(6,36)} = 4.22$, $p < 0.01$).

The analysis of number of visits showed that the mice in P2 group were less active by entering less arms (effect of group: $F_{(3,108)} = 3.19$, $p < 0.05$; LSD: P2 vs. control: $p = 0.058$; P2 vs. P20: $p < 0.01$) (Fig. 2). No significant main effect of time was observed but a significant effect of arm was noted, showing that all mice tended to enter the novel arm significantly more often than the other arms ($F_{(2,108)} = 54.31$, $p < 0.01$). The significant third-order interaction among arm, time and group ($F_{(12,108)} = 1.895$, $p < 0.05$) showed

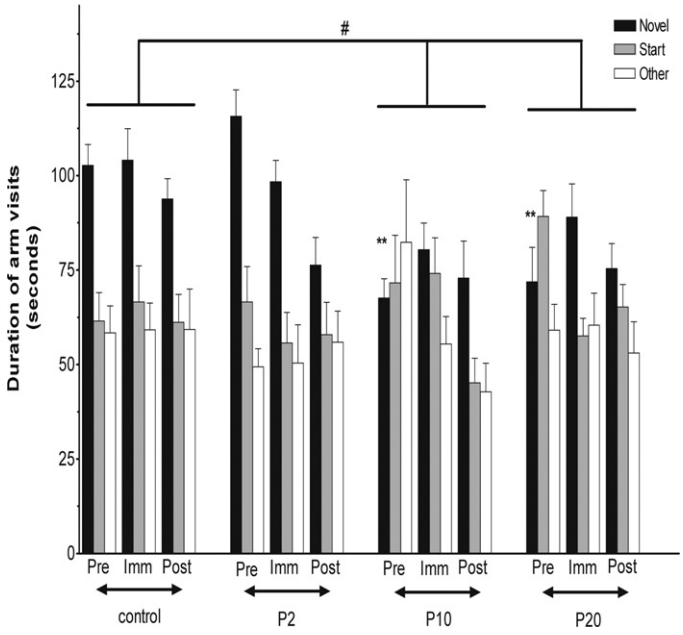

Fig. 1. Effect of propranolol treatment on spatial memory in Y-maze. Comparison of the time spent in the novel, start and other arms during 5-min test for each period (Pre, Imm, and Post). When propranolol was injected at Imm and Post, all mice spent more time in the novel arm compared to other arms, whereas when injection occurred at Pre, P10 and P20 groups did not spend more time in any arm. Data were expressed as mean ± S.E.M ($N = 10$ per group). $^{**}p < 0.01$ for difference in performance in novel arm between control and P10, P20. $\#p < 0.05$ for difference in performance in all arms between mice treated with propranolol and control.

that, when propranolol was injected at Pre, mice in P10 and P20 groups did not entry more in the novel arm compare to other arms (significant arm by group interaction, $F_{(6,36)} = 3.21$, $p < 0.01$).

Summary of different parameters measured in the open-field test were showed in Table 1. One-way ANOVA analysis indicated that propranolol significantly decreased the locomotor activity ($F_{(3,49)} = 3.96$, $p < 0.05$), and the time spent in central squares ($F_{(3,49)} = 2.74$, $p = 0.05$) and the number of defecation ($F_{(3,49)} = 5.21$, $p < 0.01$). Post hoc Fisher's LSD tests indicated that 2 mg/kg of propranolol significantly decreased the horizontal locomotion (saline vs. P2, $p < 0.05$) and time spent in central squares (saline vs. P2, $p < 0.05$); whereas the higher dose tended to decrease defecation (saline vs. P10, $p < 0.01$; saline vs. P20, $p < 0.01$) The percentage of central locomotion was decreased, but the overall effect of propranolol was not statistically significant.

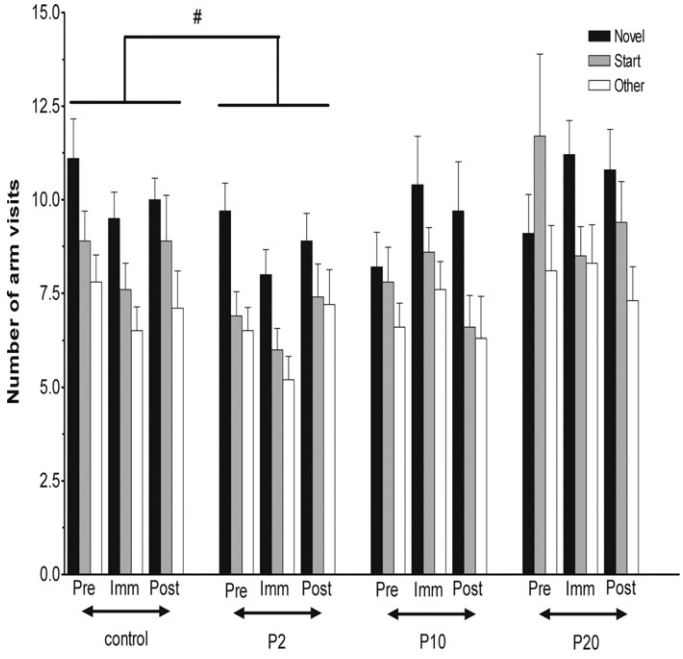

Fig. 2. Effects of propranolol treatment on the locomotor activity in Y-maze. Comparison of the number of arm visits for mice visiting the arms during 5-min test when propranolol was injected at Pre, Imm, and Post. Data were expressed as mean ± S.E.M. $\#p = 0.058$ for difference in the total number of arm visits of mice in control vs. P2.

4. Discussion

Our main finding was that memory process was unaffected when propranolol was administered to mice before testing or after training which is consistent with our previous report [38]. However when administered before the first trial (Pre), memory process was impaired. Furthermore, the degree to which memory was impaired appeared to be dose-dependent, with relatively lower dose (2 mg/kg) having no disruption, but higher doses (10 and 20 mg/kg) inducing a serious disruption of memory.

In Y maze, two measures of exploratory behavior (inspective and inquisitive) should be separately analyzed [9]. Inspective exploratory behavior is reflected in the duration spent in arms, while the number of arm visits is an index of inquisitive behavior and can measure locomotor activity as well. The main effect of treatment observed for duration and entry showed that mice in P10 and P20 visited as many arms but stayed shorter than control, while P2 group stayed in arms as long but visited less than control group. This indicated that lower dose of propranolol affected inquisitive behavior and higher doses changed inspective behavior. On the other hand, the reduced arm visits in P2 also suggested reduced locomotor activity, which was consisted with results obtained from open-field test, and also in accordance with a previous reported anxiogenic-like effect of propranolol in mice [30]. However from the present data, we only see such effect at a lower dose; why the higher doses lack such effect is still unknown, but our data suggest that lower dose of propranolol have anxiogenic-like effect with reduced locomotor activity and increased grooming while higher doses markedly decrease defecation, probably associated with a suggestive anxiolytic-like effect reported in rats [33].

Behavioral and memory-specific effects of pre-training systemic administration of beta-blocker propranolol have been studied in several studies. Functional inactivation of the LC impairs acquisition in the Morris water maze in rat [18] and distinct roles for different β-adrenoreceptor in memory processing has been suggested, with β1-adrenoreceptor specifically modulating acquisition of short-term memory [14]. Furthermore, it has been shown that propranolol could inhibit novelty-induced LTD and learning-facilitated LTP which encode different aspects of spatial environment, thus upon re-exposure to the "familiar" environment, the propranolol-treated animals behave as if they have never seen this environment before [17]. Our results are in agreement with those studies in that pre-training administration of propranolol selectively impaired memory acquisition. It is reasonable for us to suggest that in our experiment, changes in arousal triggered by exploration of Y-maze result in β-adrenoreceptor activation and facilitate synaptic plasticity, while propranolol may interrupt with that novelty-induced synaptic plasticity at the time of learning and block familiarization to the novel spatial environment.

Propranolol has been suggested to impair memory consolidation [4,16,22] and retrieval process [24] in both positively and negatively reinforced tasks in rats, however we did not find its effect on consolidation and retrieval of spatial recognition memory in mice at the present study. The reason for the discrepancies is

Table 1
Summary of the parameters measured in the open-field test.

Open-field	Horizontal locomotion (m)	Inside square (s)	Central field penetration	Rearing	Grooming	Defecation
Group						
Saline	37.89 ± 0.91	39.6 ± 4.03	22.15 ± 2.48	48.92 ± 3.54	1.92 ± 0.24	2.15 ± 0.41
P2	34.63 ± 1.1*	27.7 ± 5.13*	18.75 ± 3.01	47.92 ± 3.45	2.58 ± 0.36	1.91 ± 0.34
P10	38.41 ± 1.01	33.5 ± 4.42	24.42 ± 2.85	45.67 ± 3.22	2.17 ± 0.27	0.83 ± 0.17*
P20	37.48 ± 0.52	30.3 ± 2.29	20.23 ± 1.91	53.46 ± 2.57	2.00 ± 0.42	0.85 ± 0.24*

Each value is expressed as mean ± SEM. (saline, P20: $N = 12$; P2, P10: $N = 13$).
* Indicates that there was a significant difference between Saline group and Propranolol group ($p < 0.05$, One-way ANOVA).

unknown, but differences in results may be due to varying patterns of different animal models selected and different behavior tasks used. For example, post-learning systemic administration of propranolol selectively impaired memory consolidation in rats causing "good learner" a robust retrograde amnesia, while "poor learners" left unaffected [4]. Another study showed that systemic or intra-amygdala infused propranolol blocked reconsolidation but not consolidation of auditory fear conditioning [8], while the same dose affected consolidation of inhibitory avoidance [27]. On the other hand, NE released in emotional tasks was the reinforcing stimulus responsible for the subsequent storage of memory. Compared with those stressful tasks such as water maze, the endogenous level of NE in the Y-maze may be relatively low, thus the mechanism involved in noradrenergic regulation of memory may be different. In addition, it has been established that memory consolidation has a time window [21], the gradient for which is not always monotonic and is task dependent, and accordingly, the temporal dynamics of regulation of memory consolidation by propranolol is task dependent. However, since we only test the effects of treatments shortly after training, our finding do not rule out the possibility that noradrenergic transmission may be still involved in a later phase of consolidation and propranolol may also need more time to manifest its effect [29,35].

Propranolol has been implicated in learning and memory processes for a variety of emotional tasks [36] in both humans and laboratory animals, however our study indicates a disruption of learning ability in a non-aversive, novelty-based spatial task. Studies utilizing additional selective adrenergic blocking drugs and considering both the time and way of drug administration should greatly clarify the nature of adrenergic participation in memory processes. As propranolol is clinically relevant and readily available for studies in humans, further investigation concerning its precise mechanism in memory is of significant theoretical and clinical importance, and has important implications in the context of everyday human cognition.

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References

[1] C.W. Berridge, B.D. Waterhouse, The locus coeruleus-noradrenergic system: modulation of behavioral state and state-dependent cognitive processes, Brain Research Brain Research Reviews 42 (2003) 33–84.
[2] G. Bianchetti, J.L. Elghozi, R. Gomeni, P. Meyer, P.L. Morselli, Kinetics of distribution of di-propranolol in various organs and discrete brain areas of the rat, The Journal of Pharmacology and Experimental Therapeutics 214 (1980) 682–687.
[3] L. Cahill, B. Prins, M. Weber, J.L. McGaugh, Beta-adrenergic activation and memory for emotional events, Nature 371 (1994) 702–704.
[4] L. Cahill, C.A. Pham, B. Setlow, Impaired memory consolidation in rats produced with beta-adrenergic blockade, Neurobiology of Learning and Memory 74 (2000) 259–266.
[5] C.D. Conrad, L.A. Galea, Y. Kuroda, B.S. McEwen, Chronic stress impairs rat spatial memory on the Y maze, and this effect is blocked by tianeptine pretreatment, Behavioral Neuroscience 110 (1996) 1321–1334.
[6] D. Dahl, J. Li, Long-lasting potentiation and depression by novel isoproterenol and cholecystokinin 8-S interactions in the dentate gyrus, Experimental brain research. 100 (1994) 155–159.
[7] D Dahl, J.M. Sarvey, Norepinephrine induces pathway-specific long-lasting potentiation and depression in the hippocampal dentate gyrus, Proceedings of the National Academy of Sciences of the United States of America 86 (1989) 4776–4780.
[8] J. Debiec, J.E. Ledoux, Disruption of reconsolidation but not consolidation of auditory fear conditioning by noradrenergic blockade in the amygdala, Neuroscience 129 (2004) 267–272.
[9] F. Dellu, W. Mayo, J. Cherkaoui, M. Le Moal, H. Simon, A two-trial memory task with automated recording: study in young and aged rats, Brain Research 588 (1992) 132–139.
[10] F. Dellu, A. Contarino, H. Simon, G.F. Koob, L.H. Gold, Genetic differences in response to novelty and spatial memory using a two-trial recognition task in mice, Neurobiology of Learning and Memory 73 (2000) 31–48.
[11] B. Ferry, J.L. McGaugh, Clenbuterol administration into the basolateral amygdala post-training enhances retention in an inhibitory avoidance task, Neurobiology of Learning and Memory 72 (1999) 8–12.
[12] S.L. Foote, F.E. Bloom, G. Aston-Jones, Nucleus locus ceruleus: new evidence of anatomical and physiological specificity, Physiological Reviews 63 (1983) 844–914.
[13] M.E. Gibbs, R.J. Summers, Role of adrenoceptor subtypes in memory consolidation, Progress in Neurobiology 67 (2002) 345–391.
[14] M.E Gibbs, R.J. Summers, Contrasting roles for beta1, beta2 and beta3-adrenoceptors in memory formation in the chick, Neuroscience 131 (2005) 31–42.
[15] M.G. Griffin, G.T. Taylor, Norepinephrine modulation of social memory: evidence for a time-dependent functional recovery of behavior, Behavioral Neuroscience 109 (1995) 466–473.
[16] J.Z. Ji, X.H. Zhang, B.M. Li, Deficient spatial memory induced by blockade of beta-adrenoceptors in the hippocampal CA1 region, Behavioral Neuroscience 117 (2003) 1378–1384.
[17] A. Kemp, D. Manahan-Vaughan, Beta-adrenoreceptors comprise a critical element in learning-facilitated long-term plasticity, Cerebral Cortex 18 (2008) 1326–1334.
[18] B. Khakpour-Taleghani, R. Lashgari, F. Motamedi, N. Naghdi, Effect of reversible inactivation of locus ceruleus on spatial reference and working memory, Neuroscience (2008).
[19] V. Kitchigina, A. Vankov, C. Harley, S.J. Sara, Novelty-elicited, noradrenaline-dependent enhancement of excitability in the dentate gyrus, The European Journal of Neuroscience 9 (1997) 41–47.
[20] J.E. Lisman, N.A. Otmakhova, Storage, recall, and novelty detection of sequences by the hippocampus: elaborating on the SOCRATIC model to account for normal and aberrant effects of dopamine, Hippocampus 11 (2001) 551–568.
[21] J.L. McGaugh, Memory—a century of consolidation, Science New York N. Y 287 (2000) 248–251.
[22] J.L. McGaugh, The amygdala modulates the consolidation of memories of emotionally arousing experiences, Annual Review of Neuroscience 27 (2004) 1–28.
[23] M.Y. Min., H.W. Yang., Y.W. Lin, Role of the Noradrenergic System in Synaptic Plasticity in the Hippocampus. Novel Trends in Brain Science, Springer, Japan, 2008, 149–164.
[24] C.F. Murchison, X.Y. Zhang, W.P. Zhang, M. Ouyang, A. Lee, S.A. Thomas, A distinct role for norepinephrine in memory retrieval, Cell 117 (2004) 131–143.
[25] K.A. Nielson, D.A. Czech, K.K. Laubmeier, Chronic administration of propranolol impairs inhibitory avoidance retention in mice, Neurobiology of Learning and Memory 71 (1999) 248–257.
[26] A. Pertovaara, Noradrenergic pain modulation, Progress in Neurobiology 80 (2006) 53–83.
[27] G.L. Quirarte, B. Roozendaal, J.L. McGaugh, Glucocorticoid enhancement of memory storage involves noradrenergic activation in the basolateral amygdala, Proceedings of the National Academy of Sciences of the United States of America 94 (1997) 14048–14053.
[28] S.J. Sara, C. Dyon-Laurent, A. Herve, Novelty seeking behavior in the rat is dependent upon the integrity of the noradrenergic system, Brain Research Cognitive Brain Research 2 (1995) 181–187.
[29] S.J. Sara, P. Roullet, J. Przybyslawski, Consolidation of memory for odor-reward association beta-adrenergic receptor involvement in the late phase, Learning & memory Cold Spring Harbor, N. Y 6 (1999) 88–96.

[30] E.A. Stone, S.J. Manavalan, Y. Zhang, D. Quartermain, Beta adrenoceptor blockade mimics effects of stress on motor activity in mice, Neuropsychopharmacology 12 (1995) 65–71.
[31] T. Straube, J.U. Frey, Involvement of beta-adrenergic receptors in protein synthesis-dependent late long-term potentiation (LTP) in the dentate gyrus of freely moving rats: the critical role of the LTP induction strength, Neuroscience 119 (2003) 473–479.
[32] T. Straube, V. Korz, D. Balschun, J.U. Frey, Requirement of beta-adrenergic receptor activation and protein synthesis for LTP-reinforcement by novelty in rat dentate gyrus, The Journal of Physiology 552 (2003) 953–960.
[33] A. Stuchlik, T. Petrasek, K. Vales, A dose-response study of the effects of pretest administration of beta-adrenergic receptor antagonist propranolol on the learning of active place avoidance, a spatial cognition task, in rats, Behavioural Brain Research 200 (2009) 144–149.
[34] R.M. Sullivan, J.L. McGaugh, M. Leon, Norepinephrine-induced plasticity and one-trial olfactory learning in neonatal rats, Brain Research 60 (1991) 219–228.
[35] S. Tronel, M.G. Feenstra, S.J. Sara, Noradrenergic action in prefrontal cortex in the late stage of memory consolidation, Learning & Memory Cold Spring Harbor, N. Y 11 (2004) 453–458.
[36] A.H. van Stegeren, The role of the noradrenergic system in emotional memory, Acta Psychologica 127 (2008) 532–541.
[37] A Vankov, A. Herve-Minvielle, S.J. Sara, Response to novelty and its rapid habituation in locus coeruleus neurons of the freely exploring rat, The European Journal of Neuroscience 7 (1995) 1180–1187.
[38] J. Zhang, J. He, Y.M. Chen, J.H. Wang, Y.Y. Ma, Morphine and propranolol coadministration impair consolidation of Y-maze spatial recognition memory, Brain Research 1230 (2008) 150–157.