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The Role of Beta-Adrenergic System on the Enhancement of Spatial Learning Caused by Glucose Injection in Young Male Rats

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Abstract: This study was designed to evaluate the role of beta-adrenergic system on the enhancement of spatial learning caused by glucose injection in the Y-maze. Young male Wistar rats were given daily injections of glucose (500 mg kg^{-1}, i.p.) 10 min before training, propranolol (20 mg kg^{-1}, s.c.) 30 min before training and co-administration of glucose (500 mg kg^{-1}) and propranolol (20 mg kg^{-1}). Three sham groups were received saline at the same volume and conditions. Comparison between co-administration of glucose and propranolol and glucose groups, showed a significant differences at first ($p<0.01$), third ($p<0.001$), fourth ($p<0.01$) and fifth ($p<0.001$) days. Indeed, co-administration of glucose and propranolol caused impairment of spatial learning. There was no significant difference between propranolol and co-administered groups. These findings indicate that propranolol impairs improvement of spatial learning caused by glucose administration via blockade of beta-adrenergic receptors and thus it seems that glucose exerts its memory enhancing effects via beta-adrenergic receptors.

Key words: Glucose, propranolol, beta-adrenergic system, spatial learning, Y-maze

INTRODUCTION

The memory-improving action of glucose has now been studied for almost 20 years and the study of this phenomenon has led to a number of important developments in the understanding of memory and brain physiology (Messier, 2004). Over the past several years, considerable evidence has accumulated from rodents and humans suggesting that modest increases in circulating glucose regulate many brain and behavior functions, including learning and memory (Gold, 2004, 2005; Nabb and Benton, 2006). Systemically administered drugs like D-glucose near the time of training, enhance learning and memory for a broad spectrum of tasks (Gold, 2004; McNay *et al*., 2006; Salinas and Gold, 2005). Also, glucose effectively enhances cognition in persons with Alzheimer disease or Down syndrome (Watson and Craft, 2004).

Injections of glucose prior to behavioral testing enhance memory and block the testing-associated drop in ECF glucose in the hippocampus (Messier, 2004; Gold, 2005).

The hippocampus that is an important brain region involved in the acquisition and consolidation of spatial learning, has one of the denser inputs of adrenergic terminals in the central nervous system, supporting hypotheses suggesting that the adrenergic system plays a role in learning and memory (Morris *et al*., 2003; Schroeter and Apparsundaram, 2000).

Studies that investigate the role of adrenergic system in learning and memory processes, specially consider the role of beta-adrenergic system in this field. Beta-adrenoceptors in area CA1 of hippocampus are involved in regulating *in vivo* synaptic plasticity of this area and are important for spatial learning (Jinzhao *et al*., 2003). Also, substantial evidence from animal studies suggests that enhanced memory associated with emotional arousal, results from an activation of beta-adrenergic stress hormone systems during and after an emotional experience (Cahill *et al*., 1994). Also, findings of many studies indicate that beta-adrenergic system interacts with other neuromodulatory systems including opioid peptidergic, GABAergic, cholinergic and muscarinic systems in the regulating memory processes (Berlau and McGaugh, 2006; McGaugh and Cahill, 1997; Saber and Cain, 2003; Salinas *et al*., 1997; Watabe *et al*., 2000).

Although glucose improvement of memory is well established, there are controversial reports in this ground. For example, as suggested by Ragozzino *et al*. (1992), glucose (100 mg kg^{-1}) did not enhances Y-maze spontaneous alternation performance, when injected intra-septally.

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In consider to the controversial reports, researches to reverse these controversies also determining the mechanism by which glucose exerts its memory improving effect have been continued. So, in regard to the definite role of beta-adrenergic receptors in the spatial learning, in this study, the possibly role of adrenergic system in the memory-enhancing effects of glucose have been evaluated.

MATERIALS AND METHODS

Animals: Male wistar rats, weighting 90±30 g, were prepared from animal house of Jundishapour University. The rats were individually housed in a clean room, with constantly controlled temperature (23±1°C) and light (12 h light-dark cycles, with lights on at 8:00) and free access to tap water and pelleted food. They were held in the colony room for 2 days before training. All experimental manipulations were carried out during the light period from 07:00 am to 06:00 pm.

Drug administration: Glucose was obtained from Merck Chemical Co and propranolol hydrochloride (dl) was purchased from Sigma Chemical Co (st.louis, Mo). They prepared in sterile 0.9% NaCl vehicle. Five hundred milligram per kilogram glucose (Ebrahimy vostakolaee *et al*., 2002) was administered by i.p. injection and 20 mg kg^{-1} propranolol (Sullivan *et al*., 1989) was administered by s.c injection daily for 5 days prior to onset of training and testing and was continued on the same schedule throughout the duration of experiment. During behavioral manipulations on training days, glucose was injected 10 min and propranolol was injected 30 min before training. Rats randomly were divided into 7 groups:

Control group as no injection group was trained only, glucose injection group, propranolol injection group, co-administration of glucose and propranolol and three sham groups were received saline at the same volume and conditions.

Blood glucose level: Blood glucose concentration in control, sham and glucose groups were determined 10 min after injection of glucose (500 mg kg^{-1}) or saline. The mean of blood glucose concentration were 110 mg dL^{-1} in control, 98 mg dL^{-1} in sham and 140 mg dL^{-1} in glucose groups.

Apparatus: A Y-maze apparatus was used for active avoidance conditioning (Ebrahimy vostakolaee *et al*., 2002). The Y-maze was composed of three equally spaced, through shaped arms joined to a triangular central platform. Each arm was 60 cm in length and 17.5 cm in height, with a floor width of 3.5 cm and a ceiling width of 14 cm. the ceiling was covered with translucent black Plexiglas (Stefani and Gold, 2001).

Behavioral testing procedures: To begin each experimental session, the animal was transported in its living cage from the colony room to the testing room. After a few minutes, the animal was transferred to the unit and procedures were initiated as follows. Y-maze apparatus was put in a completely dark and silent place. To knowing the apparatus, at the first day of the training, rats were allowed to have a freely moving for 15 min. Then, training was begin from the arm that rat was there. Each rat was trained 30 trials every day and training was continued for 5 days. At the end of each session, Correct Response Percentages (CRP) were calculated. Minimum CRP was considered as 86.6% (Moazedi and Motamedi, 1995).

Statistical analyses: Data were analyzed with SPSS software (ver: 10.0) using One Way ANOVA procedure, then for determining the significant difference between groups, Least Significant Difference (LSD) procedure were used. The minimally acceptable level was set at $p<0.05$.

RESULTS AND DISCUSSION

The results showed that there is a significant difference between glucose (n = 7) and sham (n = 7) groups at the first day ($p<0.05$) of training. Indeed, glucose injection caused improvement of spatial learning (Fig. 1). Also, comparison between propranolol (n = 8) and sham groups (n = 7) show a significant difference at the fifth day ($p<0.001$) that revealed impairment of spatial learning by propranolol injection (Fig. 2). On the other hand, comparison between co-administration of glucose and propranolol group (n = 8) with glucose group, show

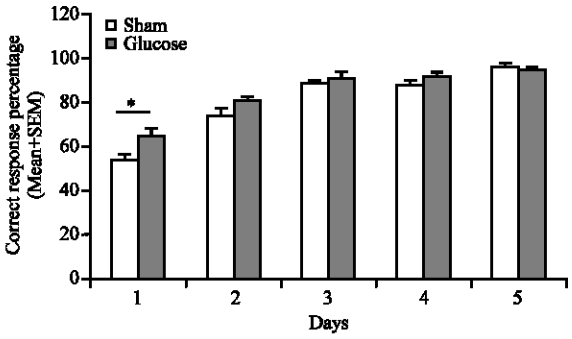

Fig. 1: The effect of glucose administration on correct response percentage (Mean±SEM) in the 5 days of training *: $p<0.05$

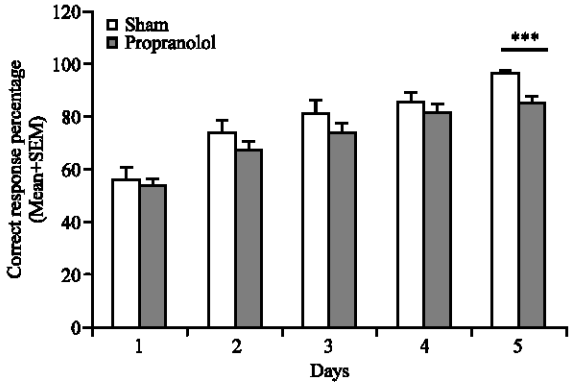

Fig. 2: The effect of propranolol administration on correct response percentage (Mean±SEM) in the 5 days of training ***: p<0.001

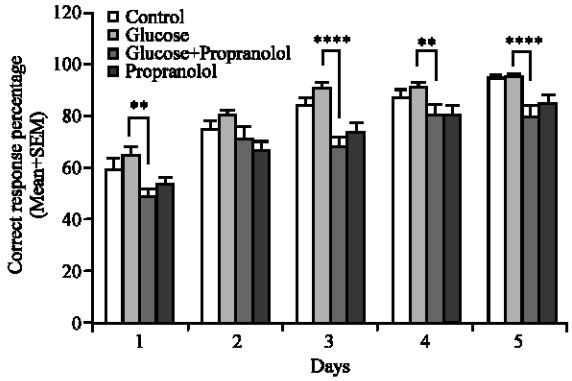

Fig. 3: Comparison between the mean of correct response percentage (Mean±SEM) in the 5 days of training of glucose, propranolol and co-administration of glucose and propranolol **: p<0.01 ****: p<0.001

significant differences at first (p<0.01), third (p<0.001), fourth (p<0.01) and fifth (p<0.001) days of training and as we see in Fig. 3, the mean of correct response percentage in co-administered is lower than glucose group. There was no significant difference between propranolol and co-administered groups (Fig. 3).

In this study, the role of beta-adrenergic system in the enhancement of spatial learning induced by glucose was investigated. The results showed that glucose injection causes improvement of spatial learning in young male rats and this result, confirms several reports of other researchers. According to Gold (2005), administration of glucose enhances cognitive functions in humans and rodents, including reversing age-related impairments in learning and memory. In addition, systemic injections of glucose enhance memory for a remarkably wide range of tasks. For example, glucose enhances memory on several, primarily verbal, memory tasks in humans (Messier, 2004; Watson and Craft, 2004) and enhances learning and memory in inhibitory and active avoidance as well as spontaneous alternation test (Gold, 2004). On the other hand, there are controversial reports about the positive effect of glucose on spatial learning. As shown by Gold *et al.* (1986), post training injection of glucose (100 mg kg^{-1}, s.c) to Spragu-Dawley rats, impairs memory for an aversive task when the electric shock use to motivate animal is a high-intensity shock (0.7 mA, 3.4 sec) while facilitates memory for an aversive task when the electric shock uses to motivate animal is a low intensity shock (0.5 mA, 0.7 sec).

The mechanisms of glucose's actions on memory have been under intense investigation for the past several years. It seems unlikely that glucose affects cognition via only one mechanism and findings indicate that it is possible that both central and peripheral mechanisms operate to produce the optimal physiological states that will lead to memory facilitation (Messier, 2004). Glucose freely crosses the blood-brain barrier (Pych *et al.*, 2006) via its transporters. So, it is plausible that glucose affects central processes directly to modulate memory performance (Messier, 2004; Stefani *et al.*, 1999). Microinjections of glucose directly into the lateral ventricles of the brain, hippocampus (Stefani and Gold, 2001), medial septum (Stefani and Gold, 1998) or amygdala (Schroeder and Packard, 2003) also enhance memory and reverse drug-induced impairments in learning and memory (Korol and Gold, 1998; McNay *et al.*, 2006; Berridge and Waterhouse, 2003). The other possible mechanism by which glucose exerts it's effect, is the enhancement of acetylcholine (Ach) release in the brain in learning and memory situations and conclude that cholinergic system is involved in glucose regulation of learning and memory and other cognitive functions (Korol and Gold, 1998; Gulpinar and Yegen, 2004).

The second possible mechanism for a glucose-mediated peripheral sensor, involves glucose-sensitive neurons (Messier, 2004; McNay and Gold, 2002). Also, Glucose can affects memory processes via K-ATP channels. This class of inwardly rectifying potassium channel is present in the mammalian brain and expresses at high levels in the hippocampus (McNay and Gold, 2002; Stefani *et al.*, 1999). In addition, there are in the cortex, striatum and septal region (Stefani *et al.*, 1999; Rashidy-pour, 2001).

Also, present results showed that propranolol injection causes impairment of spatial learning in young male rats and this result confirms other studies in this field. Agents that alter adrenergic receptors, such as beta-blockers, also alter memory storage (Nielson *et al.*, 1999; Czech *et al.*, 2000). Different studies indicate that

administration of propranolol, in fact blockade of beta-adrenoceptors, impairs memory for inhibitory avoidance, odor-reward association and spatial learning in water maze and radial maze in animals and for an emotionally arousing story in humans (Nielson *et al*., 1999; Ji *et al*., 2003; Zarrindast *et al*., 2004). The fact that administration of DL-propranolol pretraining (Jinzhao *et al*., 2003) and immediately posttraining (Ji *et al*., 2003), impairs spatial learning also long-term spatial memory suggests that beta-adrenoceptors in area CA1 are engaged in the neural mechanism underlying memory consolidation. On the other hand, there are controversial reports about the effect of propranolol on spatial learning. As shown by Decker *et al*. (1990) acute pretraining systemic administration of propranolol (10 mg kg^{-1}) has been reported not to affect spatial memory in the Morris Water Maze. The effects of chronic propranolol specifically on endogenous memory modulation are virtually unknown (Nielson *et al*., 1999; Czech *et al*., 2000), while it could has profound qualitative effects on such cognitive processing. Although propranolol and other beta-adrenergic antagonists most commonly do not directly impair memory, they have been shown to interfere with modulatory processes affecting memory consolidation. Chronic propranolol treatment significantly impairs endogenous memory systems, which normally function to distinguish important events from trivial ones (Nielson *et al*., 1999). The chronic effects of propranolol may involve either adrenergic and serotonergic mechanisms or secondary effects on other systems to which they are linked (e.g., cholinergic effects). A number of possible mechanisms that may be engaged in the chronic effects of propranolol on retention, perhaps involving cholinergic systems, which have notable memory-related interactions with adrenergic systems (Czech *et al*., 2000). It is possible that long-term treatment results in an adaptive response from beta-adrenergic or other receptor systems, as for example might be linked to up-regulation or down-regulation, or that a separate mechanism is recruited by long-term treatment that is not active in acute treatment (Czech *et al*., 2000; Terry *et al*., 1990). Blockade of beta-adrenoceptors in area CA1 by DL-propranolol may reduce the intracellular CAMP level in area CA1 and therefore attenuate the activity of the CAMP-PKA-CREB pathway that is essential for memory consolidation, inducing a deficit in memory consolidation. Also, strong evidence from animal research suggests that disruption of amygdale modulatory influences on consolidation of ipsilateral information processing may underlie the impairing effects of propranolol on memory (Cahill and Stegeren, 2003). Our results of comparison between glucose and co-administration of glucose and propranolol groups, showed an impairment of spatial learning in co-administered rather than glucose group. These findings indicate that propranolol impairs improvement of spatial learning caused by glucose via blockade of beta-adrenergic receptors and thus it seems that glucose exerts its memory enhancing effects via beta-adrenergic receptors. In addition, there is not any significant difference between propranolol and co-administered groups that confirms the above results. Extracellular concentrations of brain glucose levels and especially in hippocampus fluctuate during memory tests and these fluctuations reduce by systemic injections of glucose (Pych *et al*., 2006; Gold, 2004). Thus exogenous glucose can influences brain glucose concentrations. On the other hand as said before, the existence of beta-adrenoceptors in area CA1 that is an essential region for spatial learning is well established. Regarding to these data, it is possible that systemic injections of glucose, can influence CA1 beta-adrenoceptors by effect on the brain extracellular glucose levels in the hippocampus and glucose exerts its function on spatial learning via these beta-adrenoceptors. A possible pathway by which epinephrine exerts at least a part of its peripheral actions may involve the actions of epinephrine on hepatic stores of glucose and the subsequent penetration of glucose into the brain to affect acetylcholine release in the hippocampus (Miyashita and Williams, 2006). Epinephrine uses as agonist and propranolol uses as antagonist of beta-adrenergic receptors. After propranolol injection, this drug possibly occupies beta-adrenoceptors and prevents putting of epinephrine on these receptors. By this way, epinephrine can not enhance blood glucose levels and this amount of glucose can not enhance acetylcholine release. Thus as result, propranolol can not impair memory.

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