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Research Paper

TOTAL SLEEP DEPRIVATION COMPROMISES BLOOD–BRAIN BARRIER INTEGRITY AND IMPAIRS LEARNING AND MEMORY: A PROTECTIVE EFFECT OF GLIBENCLAMIDE AND RECOVERY SLEEP

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Abstract

The present study focused on investigating the possible neuroprotective potential of peripheral glibenclamide pretreatment and sleep recovery on sleep deprivation effects in rats and the possible mechanisms of action (s). Adult male rats were sleep deprived for a period of 3 days using grid suspended over water method. Morris water maze was used to reveal the effect of both sleep deprivation and the different treatments on learning and memory. Potential mechanisms were explored applying HPLC- UV determination of hippocampal and cortical monoamines in rats. In addition, blood brain barrier intergrity was determined in different groups using Evans blue dye extravasation method. Sleep deprivation induced learning impairment and learning deterioration and neuromotor deficit. The concentrations of 5-hydroxytryptamine (5-HT), norepinephrine (NE) and dopamine (DA) significantly decreased in both brain cortex and hippocampus after sleep deprivation Moreover, sleep deprivation increased blood brain barrier permeability and induced extravasation of the Evans Blue dye in the tested brain areas. Glibenclamide pretreatment antagonized sleep deprivation-induced learning impairment and learning deterioration, and neuromotor deficit. However, pre-treatments with glibenclamide significantly increased the concentrations of 5-HT and NE in rat cortex and hippocamps and minmized the blood brain barrier permeabilty. Moreover, recovery sleep for 48 hours remarkably antagonized sleep-adverse effects. These changes might suggest that the neurochemical changes and the impairment of blood brain barrier function are- at least partly - the underlying mechanism of adverse effects of sleep deprivation on memory and learning. In addition, the potective and restorative effects of glibenclamide and sleep recovery, respectively, against sleep deprivation might be mediated through rebalance the brain chemistry and restoring the normal function of blood brain barrier.

Key words: sleep deprivation, glibenclamide, blood brain barrier, monoamines, memory.

INTRODUCTION

Sleep is important for the maintenance of physiological homeostasis and psychological balance. Disturbance or shortening of normal sleep is associated with an irregularity of the neuroendocrine control of appetite and increased risk of diabetes [1,2]. In accordance, sleep deprivation has been reported to disturb many vital processes including gene expression related to metabolic processes, response to stress and inflammation, circadian sleep/wake cycles, regulation of cell proliferation and various signaling pathways [3].

Moreover, sleep deprivation has been reported to increase plasma glucocorticoids in both human and rodents [4], and leads to augmentation of the aging process and gradual damage to brain cells [5]. In addition, inflammation has been reported to increase blood brain barrier permeability and to play a central role in the development of numerous disorders of the central nervous system (CNS) [6]. Whereas, recovery sleep has been reported to ameliorate the adverse effects of sleep deprivation on physiological process and restore the antioxidant balance [7].

Glibenclamide is a member of the sulfonylurea class of drugs whose therapeutic benefits as oral hypoglycemic agents date back to the 1960s [8]. Sulfonylurea drugs work via inhibition of Sur1. Patients with diabetes mellitus type II (DM II) benefit from glibenclamide treatment via inhibition of KATP (Sur1–Kir6.2) channels in pancreatic β islet cells, leading to increased insulin release [8]. With its long history of safety and efficacy in treating DM II, glibenclamide has provided the foundation upon which newer diabetic mono- and combined therapies have been developed [9]. During the last decade, glibenclamide has received renewed attention due to its pleiotropic protective effects in acute CNS injury. In the CNS, glibenclamide primarily inhibits the recently characterized sulfonylurea receptor 1–transient receptor potential melastatin 4 (Sur1–Trpm4) channel [10] and, in some cases, microglial Sur1–Kir6.2 (KATP) channels [16,17]. Several preclinical studies have found glibenclamide to be an effective treatment in rodent models of ischemic stroke [11-17], and retrospective studies suggest that being on a sulfonylurea drug and staying on it following ischemic CNS insults significantly improves outcomes [18,19]. The successes of these preclinical experiments [20] have set the stage for clinical trials examining glibenclamide's protective effects following ischemic strokes [21-23]. Normally, glibenclamide does not penetrate BBB [24]. However, penetration into the brain is likely due to the dysfunctional BBB leading to passive uptake of glibenclamide into brain tissues[25]. The purpose of the study is to evaluate the possible potential uses for glibenclamide against sleep deprivation's adverse effects and the probable ameliorative effect of sleep recovery.

MATERIALS & METHODS

Animals:

Sprague Dawley rats (200±30g) were obtained from the animal house of the National Organization for Drug Control and Research (NODCAR), Egypt. The animals were kept under standard laboratory conditions of light/dark cycle (12h /12h) and temperature (25 ± 2C°). They were provided with a nutritionally adequate standard laboratory diet. All experiments were carried out in accordance with institutional guidelines established by the animal care and use committee of the National Organization for Drug Control and Research (NODCAR), Egypt.

Chemicals: All chemicals Glibenclamide (Glyburide) were purchased form sigma-Aldrich Chemical Co. (St. Louis, MO, USA). Glibenclamide was freshly prepared (5mg/10 ml dimethylsulfoxide, (DMSO) and administered a single daily dose of 5mg/kg [26].

Experimental design:

A total number of 80 rats were used in the study and divided equally into two sets, one for the biochemical and behavioral study and the other for blood brain barrier study. Each set is divided into five groups, the first is control group, where the animals had normal sleep; the second is (GL) group, the animals were administered glibenclamide (5mg/ kg, p.o, day) for 6 days; the third is sleep deprivation (SD) group, the animals sleep deprived for 3 days; the fourth is sleep deprivation and glibenclamide (SD+GL) group, the animals were administered glibenclamide (5mg/ kg, p.o, day) for 6 days, starting 3 days before sleep deprivation for 3 days;

and the fifth is recovery sleep (RS) group, the animals were allowed to have normal sleep for two days after sleep deprivation for 3 days.

METHODS

Under sleep deprivation

Animals were sleep deprived for 3 days by placing them on a grid suspended over water [27]. Briefly, they were placed on a grid floor (29×15×7 cm) inside the plastic cage filled with water to 1 cm below the grid surface. The stainless steel rods of the grid (3 mm wide) were set 2 cm apart from each other. Food and water were provided ad libitum. After sleep deprivation session, the animals from different groups were sacrificed. The animals were dissected and hearts were obtained.

Blood brain barrier integrity was determined using the method described by [28] using Evans blue (EB) dye method. In brief, after the last session of sleep deprivation, EB dye (4 ml/kg, 2%) was administered intraperitonealy and allowed to circulate for 60 min. The animals were then anaesthetized with thiopental (50mg/ kg, ip) and perfused with saline through the left ventricle at a flow rate 10 ml/ min for 15 min. until colorless fluid was obtained from the right atrium. Afterwards, the brains were removed and dissected into brain cortex and hippocampus. The brain areas were weighed and homogenized in 3.5 ml phosphate-buffered saline and vortex-mixed for 2 min after the addition of 2.5 ml of 60% trichloroacetic acid to precipitate protein. The samples were then cooled in ice for 30 min and centrifuged for 30 min at 1000 r.p.m. The absorbance of the supernatants for EB dye was measured at 610 nm with a spectrophotometer. EB dye content is expressed as µg/mg of brain tissue against a standard curve.

Brain monoamines were determined by HPLC-UV method [29]. Learning and memory studies were carried out using Morris water maze (MWM test) [30].

STATISTICAL ANALYSIS

Data presented as means ± SE. One-way ANOVA followed by LSD test were used to evaluate significant differences from the control and sleep deprived groups. $P< 0.05$ was considered to be statistically significant. Statistical processor system support (SPSS) for Windows software, release 10.0 (SPSS, Inc, Chicago, IL) was used.

RESULTS

Monoamines:

Tables 1 and 2 show that sleep deprivation significantly ($p<0.05$) decreased monoamines (DA, NE and 5-HT) content in brain cortex and hippocampus. Glibenclamide pretreatment significantly minimized the decreasing effect of sleep deprivation on the tested monoamines content in brain cortex and hippocampus. Recovery sleep significantly attenuated the decreasing effect of sleep deprivation on monoamines levels. Monoamines levels of glibenclamide treated naïve (normal sleep) rats did not differ from control group.

Blood brain barrier permeability

Data in table 3 showed that sleep deprivation induced significant increase in blood brain barrier permeability in the tested brain areas. Both glibenclamide pretreatment and recovery sleep ameliorated the adverse effect of sleep deprivation. Results of glibenclamide treated naive (normal sleep) rats did not differ from control group.

Morris water maze test

Sleep deprived rats showed poor performance in Morris water maze, in terms of increased latency to reach the hidden platform, least time spent in the target quadrant in the probe test and increased latency in the visibility test. Both glibenclamide pretreatment and recovery sleep ameliorated the adverse effect of sleep deprivation on the behavioral performance in Morris water maze test. Glibenclamide treated naive (normal sleep) rats did not differ from control group (figures 1,2,3).

DISCUSSION

In the present study, the reducing effect of sleep deprivation on catecholamines (DA and NE) and serotonin levels in the brain cortex and hippocampus might be due to an inhibited synthesis resulted from mitochondrial dysfunction and/or excessive turnover of the monoamines. In accordance, an immunohisto-chemical study demonstrated that sleep deprivation decreases tyrosine hydroxylase content, the key enzyme in dopamine synthesis, in the striatum and the hypothalamus of mammals (rats) [31]. Since dopamine is the immediate precursor of epinephrine and norepinephrine, so it is likely that the decrease in catecholamines levels is due to inhibited synthesis rather than active turnover. On the other hand, sleep deprivation has been found to increase serotonin turnover in the hypothalamus and hippocampus of rats [32]. Glibenclamide protective effect might be due to mitochondrial activation. The restorative effect of recovery sleep might reflect the regenerative power of sleep and its role in the removal of the toxic byproducts of wakefulness [33-35].

Sleep deprivation compromised blood brain barrier integrity and caused extravasations of Evans blue into brain tissues. One might suggest that sleep deprivation activate an inflammatory reactions leading to brain barrier dysfunction. This can be interpreted that inflamed endothelium could secrete proinflammatory cytokines, accompanied with the activated macrophages which produce numerous factors that are injurious to the cerebrovascular endothelium. This, in turn, could lead to the increased permeability of the blood-brain barrier. In accordance, several studies indicated that sleep restriction or deprivation impairs blood-brain barrier function, most likely through inflammation [34,35]. In accordance, sleep restriction to four hours for three consecutive nights was found to increase leuckocytic count, mainly neutrophils in young healthy men [36]. Also, sleep deprivation has been found to elevate parameters of humoral immunity, including serum IgG, IgA, IgM, and cytokines C3 and C4 [37]. Acute total and short-term partial sleep deprivation resulted in elevated high-sensitivity C- reactive protein (CRP) concentrations, a stable marker of inflammation that has been shown to be predictive of cardiovascular morbidity [38-40]. It is likely that inadequate sleep might affect the functioning of the lining inside the blood vessels and can cause some low-grade inflammation that could lead to increased blood brain barrier permeability [34]. Moreover, the observation that recovery sleep considerably reversed the effect of sleep deprivation and restored the normal permeability might indicate that the effect of sleep deprivation is temporally and reversible. The ameliorative effect of glibenclamide treatment to blood brain barrier may be mediated through its inflammatory and/or its hypoglycemic effect. It is worthy to note that glibenclamide is a member of the sulfonylurea drug which work via inhibition of Sur1. Sur1 inhibition has demonstrated novel protective anti-inflammatory effects in pre-clinical models of subarachnoid hemorrhage [41]. Consistently, targeted inhibition of Sur1-regulated channels by the sulfonylurea glibenclamide (also known as glyburide) may offer an effective new treatment option for both ischemic and hemorrhagic forms of stroke [8].

The present study indicated that sleep deprivation deteriorated learning and memory and induced sensory motor deficiency. These effects might be due to the disturbances in the levels of brain monoamines,. In accordance, several studies indicated that sleep is involved in learning and memory processes [34,42,43]. Support for this theory comes from experiments showing the importance of sleep after learning, and the deleterious effect of sleep deprivation on subsequent learning [44,45]. Consistently, several studies showed that sleep deprivation produces memory deficits in learning models [44,46,47], by interfering with cAMP signaling in the hippocampus [48]. Glibenclamide treatment significantly antagonized the deleterious effect of sleep deprivation on memory and learning and the sensorimotor coordination may be due to its regulating effect energy and glucose homeostasis. Consistently, rodent studies have suggested that glibenclamide plays an important role in regulating energy and glucose homeostasis through ATP-sensitive potassium (KATP) channels. KATP. Intracerebroventricular (i.c.v). infusion of glibenclamide, a KATP channel blocker, increases endogenous glucose production (EGP) and modulates insulin release [49]. In addition, the monoamine depletion, might play a role in learning and memory deterioration and the loss sensoriomotor coordination due to sleep deprivation. Consistently, monoamine neurotransmitters, serotonin, noradrenaline and

dopamine had been reported to modulate many important cognitive processes such as attention, learning and memory [50].

One might suggest that The drug effect might be either directly through the drug's central effect on the brain cortex and hippocampus or indirectly through vagus nerve stimulation by the drug and its subsequent effect on the brain. The observation that glibenclamide had no effect on normal sleep rats might support the drug's direct effect. Moreover, the ameliorative effect of recovery sleep the on memory and learning might be due to the regenerative and cleaning effects of sleep.

It seems paradox that while glibenclamide does not penetrate blood brain barrier and does not accumulate in the brain [25], it has a rebalancing effect on brain mono-amines, restore blood brain barrier function and normalized memory and learning in sleep deprived rats. One might speculate that penetration of glibenclamide into the brain is likely due to the dysfunctional BBB under sleep deprivation leading to passive uptake of the drug into brain tissues. With local BBB breakdown, plasma extravasation leads to vasogenic edema, which carries glibenclamide, a highly protein bound drug, into the extravascular space. As a result, drug can be used to obtain a favorable therapeutic effect. The observation that glibeclamide did not affect either the levels of brain monoamines nor memory and learning in normally sleep rats might support this opinion. So, In the present study, BBB dysfunction and the resultant glibenclamide accessibility to the central nervous system through sleep deprivation was a prerequisite to attain the drug beneficial effect.

In conclusion, the study might suggest that brain monoamines imbalance and the impairment of blood brain barrier function are among the culprits causing the adverse effect of sleep deprivation on memory and learning. In addition, the potective and restorative effects of glibenclamide and sleep recovery, respectively, against sleep deprivation might be mediated through rebalance the brain monoamines and restoring the normal function of blood brain barrier.

Table 1. Effect of Glibenclamide (GL, 5mg/kg, p.o) and Recovery Sleep (RS) on monoamines contents in brain cortex of Sleep Deprived (SD) rats.

Groups	**Monoamines (µg/g tissue)**		
	Norepinephrine	**Dopamine**	**Serotonin**
Control	1.55 ± 0.08	2.58 ± 0.21	1.40 ± 0.12
GL	1.53 ± 0.05 $^{+}$	2.70 ± 0.07 $^{+}$	1.29 ± 0.02 $^{+}$
SD	1.09 ± 0.03 *	1.37 ± 0.13 *	0.76 ± 0.10 *
GL+SD	1.48 ± 0.01 $^{+}$	2.65 ± 0.06 $^{+}$	1.09 ± 0.03 $^{*,+}$
RS	1.52 ± 0.06 $^{+}$	2.54 ± 0.07 $^{+}$	1.43 ± 0.12 $^{+}$

Data are presented as means ± S.E. (n=8)

* Significant different from control

$^{+}$ Significant different from sleep deprived group

Table 2. Effect of Glibenclamide (GL, 5mg/kg, p.o) and Recovery Sleep (RS) on monoamines contents in Hippocampus of Sleep Deprived (SD) rats.

Groups	**Monoamines (µg/g tissue)**		
	Norepinephrine	**Dopamine**	**Serotonin**
Control	1.24 ± 0.03	1.71 ± 0.12	0.81 ± 0.06
GL	1.42 ± 0.04 $^{*,+}$	2.24 ± 0.07 $^{*,+}$	1.05 ± 0.04 $^{*,+}$
SD	1.02 ± 0.06 *	1.12 ± 0.06 *	0.56 ± 0.03 *
GL+SD	1.17 ± 0.04 $^{+}$	1.43 ± 0.05 $^{*,+}$	0.80 ± 0.03 $^{+}$
RS	1.22 ± 0.05 $^{+}$	1.68 ± 0.06 $^{+}$	0.83 ± 0.05 $^{+}$

Data are presented as means ± S.E. (n=8)

* Significant different from control

$^{+}$ Significant different from sleep deprived group

Table 3: Effect of Glibenclamide (GL, 5mg/kg, p.o) and Recovery Sleep (RS) on blood brain barrier permeability of Sleep Deprived Rats

Group	Cortex (% of Control)	Hippocampus (% of Control)
GL	106.2 ± 11.1 +	105.7 ± 12.0 +
SD	149.5 ± 7.4 *	168 ± 13.5 *
GL+ SD	111.7 ± 8.3+	114.6 ± 12.1 +
RS	108.8 ± 9.9 +	106.4 ± 8.4 +

Data are presented as means ± S.E. (n=8)
* Significant difference from control.
+ Significant difference from sleep deprived rat

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Fig.1

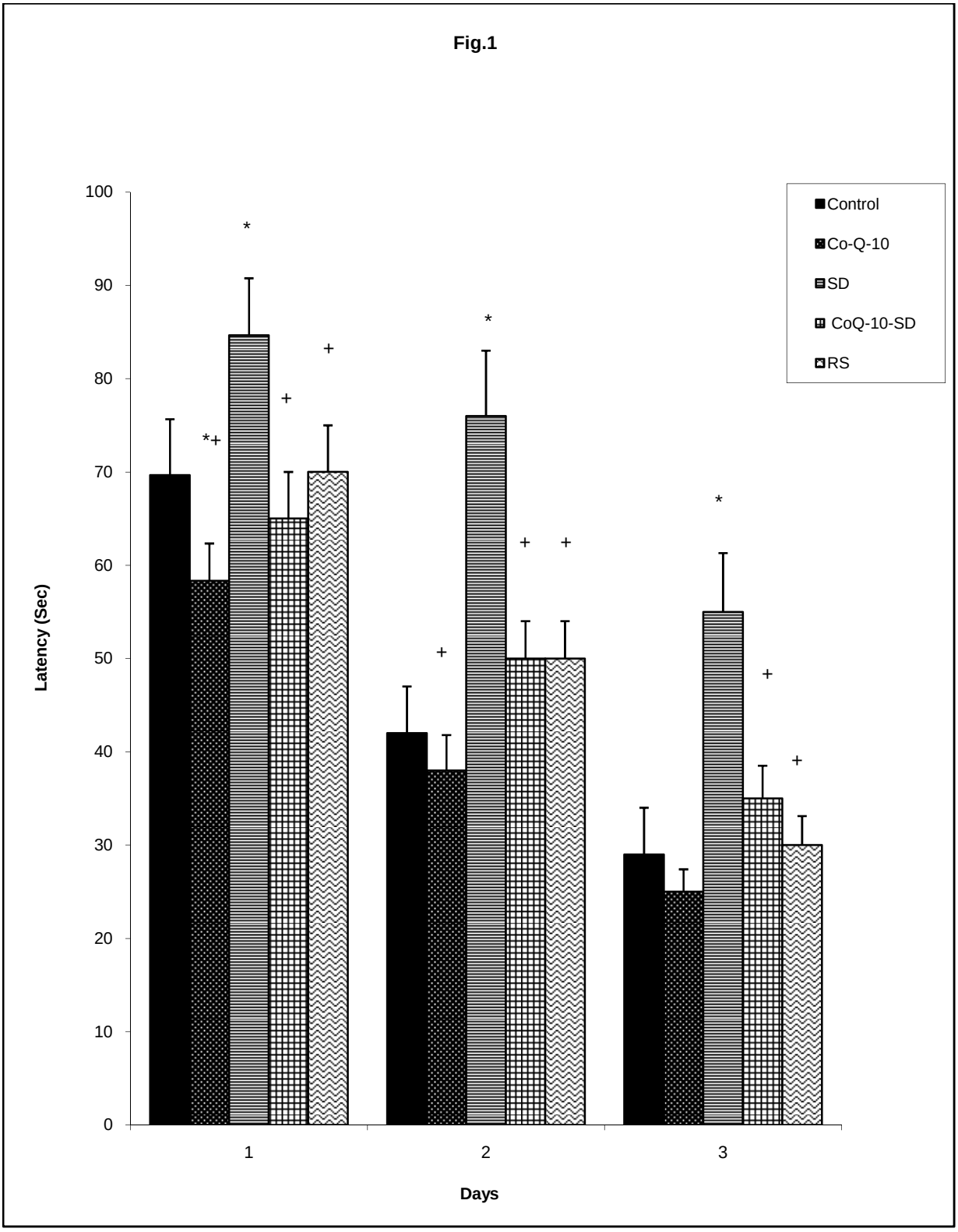

Figure 1: Effect of Glibenclamide (GL, 5mg/kg, p.o) and Recovery Sleep (RS) on Learning Ability of Sleep Deprived (SD) Rats in Morris Water Maze.
Data presented as mean± SE, (n=8), * Significant difference from control, + Significant difference from sleep deprived rats

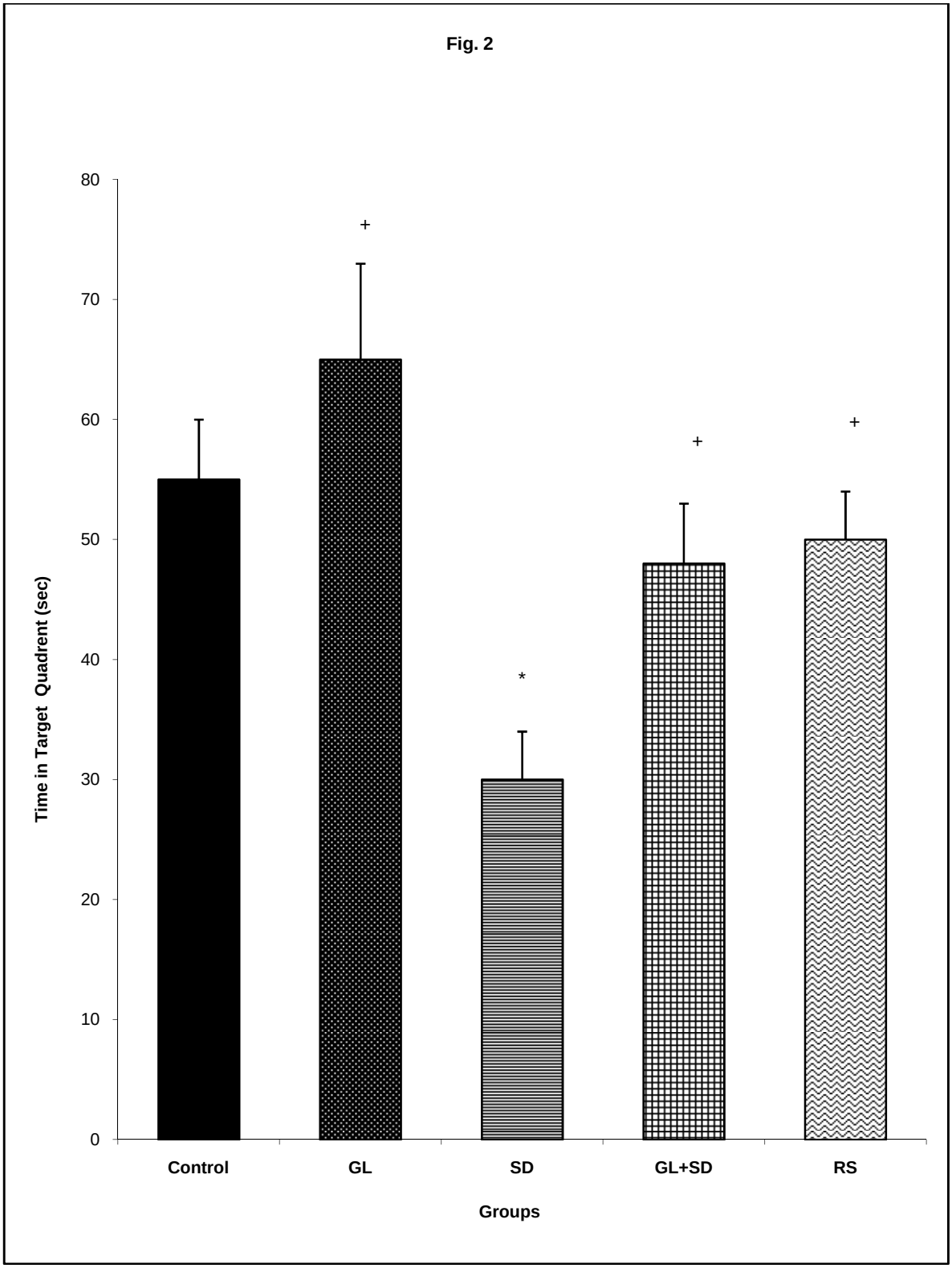

Figure 2: Effect of Glibenclamide (GL, 5mg/kg, p.o) and Recovery Sleep (RS) on Probe Test (memory test) of Sleep Deprived (SD) Rats in Morris Water Maze.
Data presented as mean± SE, (n=8).
* Significant difference from control.
+ Significant difference from sleep deprived rats

Fig. 3:

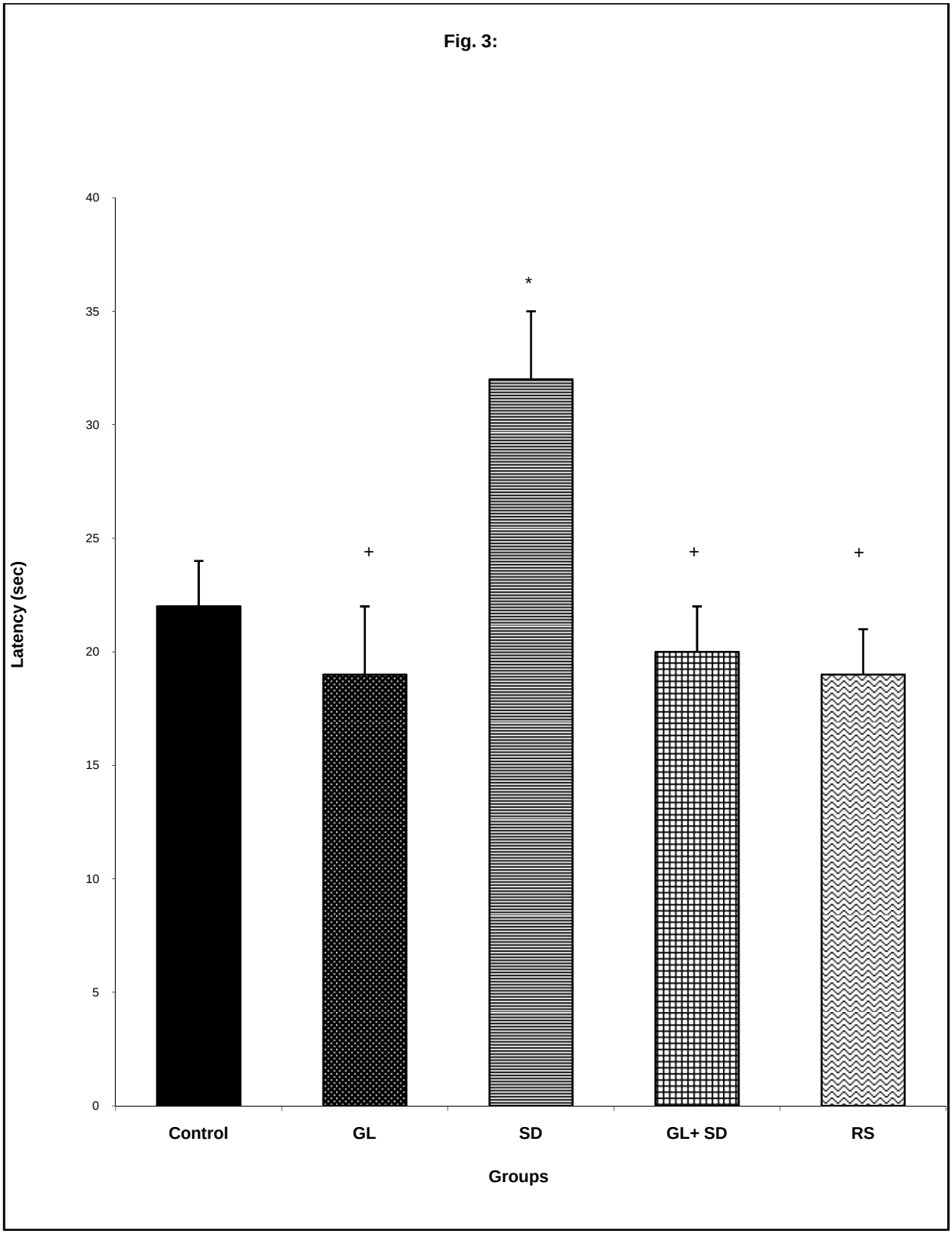

Figure 3: Effect of Glibenclamide (GL, 5mg/kg, p.o) and Recovery Sleep (RS) on Visibility Test (sensorimotor coordination) of Sleep Deprived (SD) Rats in Morris Water Maze.
Data presented as mean± SE, (n=8).
* Significant difference from control.
+ Significant difference from sleep deprived rats