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Hippocampus and Cerebellum Function Following Imipenem Treatment in Male and Female Rats: Evaluation of Sex Differences During Developmental Stage

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Abstract: The B-Lactam antibiotics have been suggested to have some degree of neurotoxicity in experimental animals as well as in clinical situations. This study has been elucidated the alteration in hippocampal and cerebellum function following adolescent imipenem exposure in male and female rats. Hippocampus and cerebellum related behavioral dysfunction in imipenem -treated [intraperitoneally, 40 and 80 mg/kg/day for one week from 23-day-old] rats were analyzed using explorative, motor function, learning and memory tasks [grasping, rotarod, open field shuttle box and Morris water maze tests]. Exposure to imipenem especially in high dosage impaired the motor coordination in male and female rats. There weren't any differences in grasping time in male and female rats. When the rearing and grooming frequency of their recorded in open field test, both males and females were dramatically affected by exposure to imipenem. Compared to the saline, male and female rats trained one week after imipenem injection showed significant memory deficits in the shuttle box and Morris water maze tests. Results in this study suggested that animals treated with imipenem suffer from motor activity and cognitive impairment. However, hippocampal and cerebellum functions of male and female rats were profoundly affected by exposure to imipenem while no sex-differences in the most variable were evident.

Key words: Imipenem, motor function, learning, memory, rat

INTRODUCTION

Nowadays many advances in medicine have occurred and one of the main fields of medical science is accurate identification of microorganisms involved in infectious diseases and their treatment with antimicrobial agents. Antibiotics are among the most common drugs used in department of pediatrics and their use for treatment of severe systemic infections in children and infants is increasing day by day. So besides life savior beneficial effects of antibiotics, study of their side effects seem to be essential.

One of the first antimicrobial agents that have been used for the therapy of infection diseases, are B-Lactams. Over time, problems such as resistance development and selection of resistant organisms have become manifest (Rodloff *et al*., 2006). Carbapenem compounds have been produced because of the medical need for compounds with broad-spectrum activity, rapid bactericidal action, limited resistance-promoting properties and good tolerability (Rodloff *et al*., 2006). Imipenem was the first carbapenem known more than two decades ago. More than 26 million patients have been treated with imipenem since that time (Rodloff *et al*., 2006; Zivanovic *et al*., 2004a). Imipenem is one of the Drugs that readily penetrate the Blood-Brain Barrier (BBB) (Suzuki *et al*., 1989). Induction of convulsions is a well-known side effect of administration of imipenem, together with the renal dehydropeptidase (DHP-I) inhibitor, cilastatin (Akisue *et al*., 1998; Dupuis *et al*., 2001; Sunagawa *et al*., 1995). However, increased use of these compounds by new patient populations can result in increasing seizure rates (Miller *et al*., 2011). Studies have been shown that seizures creation and neurotoxic properties of imipenem, is more than other B-lactams (Sunagawa *et al*., 1995), ranging from 3-33 % (Miller *et al*., 2011).

One of the proposed mechanisms of carbapenem neurotoxicity is binding of them to the Gamma-Amino Butyric Acid receptors ($GABA_A$) (Fujimoto *et al*., 1995). These receptors are ion channels with inhibitory synaptic transmission properties (Fujimoto *et al*., 1995). Many studies have been done on the drug seizure generation but there is no study about other possible neurotoxic effect of this drug, such as its effect on memory systems, motor activities and exploratory behavior. Hence, the purpose of the present study is to evaluate (1) Whether

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3hippocampal and cerebellar behavioral dysfunction occurs after intraperitoneal (i.p.) administration of imipenem and (2) The relationship between sex and behavior deficits subsequent to imipenem treatment, in rats.

MATERIALS AND METHODS

In the present study, the explorative behavioral consequences and the cerebellar and hypocampal function following i.p injection of imipenem/cilastatin [(40 mg/kg/day and 80 mg/kg/day for 7 day (two injections, each day)] have been investigated. All behavioral tests were carried out in the behavioral core facility at the neuroscience research center of kerman medical university, and the study protocol was approved by the Animal ethics committee of this institution. In this study 120 wistar rats have been used. All the animals were kept in standard conditions: temperature of 22±2°C, with a 12 h (light)-12 h (dark) cycle (lights on at 07:00). They had free access to food and water. Pups were weaned at 21 days of age. At 23 days old, these rats were randomly distributed in 16 groups (n = 10). Groups 1,2,3 and 4 consisted of male and female control groups for motor behavior and cognitive experiments ; groups 5,6,7 and 8: vehicle-treated controls (male and female saline-treated groups); groups 9,10,11 and 12 consisted of male and female imipenem/cilastatin-treated animals (40 mg/kg/day and 80 mg/kg/day, respectively) for cognitive experiments. Groups 13, 14, 15 and 16 were male and female imipenem/cilastatin-treated animals (40 mg/kg/day and 80 mg/kg/day, respectively) for motor behavior experiments. Male and female rats were housed in separate cages. Cerebellum-related behavioral dysfunction in imipenem/cilastatin-treated rats (i.p., 40 or 80 mg/kg) was analyzed using cerebellum-dependent function, motor learning, and hippocampal function tasks. Four behavioral tasks: the Morris water maze, the passive avoidance learning, the rotarod, the hanging, and open field tasks were chosen. The first behavioral test was performed 24 h after the last injection of imipenem/cilastatin. Open field, rotarod, and grasping tests were performed to screen the explorative behaviors, muscle coordination and muscle strength of rats.

BEHAVIORAL STUDIES

Morris water maze task: Animals were subjected to the Morris water maze task 7 day after the first imipenem/cilastatin (or saline) injection. This task was performed according to the methods of Shabani *et al.* (2012a). The experimental apparatus consisted of a circular water tank (160 cm wide and 45 cm high). A platform (15 cm wide and 35 cm high) was placed 1.5 cm below the surface of the water. The maze was placed in a room with extra maze visual cues. The water temperature was 21-23 °C. Data collection was automated by a video image motion analyzer (Ethovision, Noldus Information Technology, the Netherlands). In a single training protocol, each rat completed 3 blocks (each block consisted of 4 consecutive trials separated by a 30 min resting period. All of the experimental groups were tested while exposed to light (08:00 to 16:00 h). For each trial, rats were randomly released into the water from one of the 4 quadrants, facing the wall of the maze. During acquisition, the location of the platform remained constant, and rats were allowed to swim for a 60 s period to find the hidden platform. After the animal found the platform, it was allowed to remain there for 20-30 s and was then placed in a cage to rest for 20-30 s before the start of the next trial. The values for time (escape latency) and distance to find the hidden platform were collected and analyzed later. Two h after the last training trial a single probe trial was given to test the spatial memory in the water maze while the platform was removed and rat was allowed to swim for 60 s. The time and distance spent in the target quadrant (quadrant 4) were analyzed as a measure of spatial memory retention (Shabani *et al.* 2012a).

Passive avoidance learning test: The memory retention deficit was estimated in the step-through passive avoidance apparatus (Gemini, San Francisco, USA) (Haghani *et al.*, 2012). This apparatus is comprised of 2 equal compartments (20×20×20 cm) separated by a guillotine door (5×5 cm). The floor consisted of a metal grid connected to a shock scrambler. For the acquisition trial, rats were initially placed in the illuminated compartment and the door between the two compartments was opened 20 s later. The time (step-through latency) taken for each rat to enter the dark compartment was measured. Upon entering the dark compartment, the door was closed and an electrical foot shock (0.5 m for 2 sec) was delivered through the stainless steel rods.

Twenty hours after the 1st trial (the training trial), the same procedure was followed. Rats were again placed in the illuminated compartment with open door, and the latency for entering into the shock compartment (as described in the training session) was measured as Step Through Latency (STL). If a rat did not enter the dark compartment within 300 sec, it was assumed that the rat had remembered the single 'acquisition' trial experience.

Rotarod test: An accelerating rotating rod (Hugo Sachs Electronic, Germany) has been used to analyze the effects of imipenem on motor coordination and balance skills. The rotarod accelerated from a minimum speed of 10 r.m-1/rpm up to 60 r.m-1/rpm (increments of 10 r.m-1/rpm). Rats were given 3 trials with a maximum duration of 300 sec and with a 30 min intertrial rest interval, during which the length of time each animal was able to maintain its balance walking on top of the rod was measured. Animals were familiarized with the procedure 3 times prior to the start of the experiment one day, before the test Shabani *et al.* (2012b).

Wire grip test (Hanging test): The testing procedure was basically the same as that described by Shabani *et al.* (2012a) and was used to assess the muscle strength and balance. Each rat was suspended with both forepaws on a horizontal steel wire 80 cm long, diameter 7 mm. The animal was held in a vertical position when its front paws were placed in contact with the wire. When the rat grasped the wire, it was released, and the latency to fall was recorded with a stopwatch. Rats were randomly tested and each animal was given three trials with a 30 min inter-trial rest interval (Shabani *et al.*, 2012b).

Open field test: The horizontal and vertical activities of rats were recorded for a period of 5 min and then analyzed using Ethovision software (version 7), a video tracking system for the automation of behavioral experiments (Noldus Information Technology, the Netherlands). The apparatus consisted of a square arena (90 cm (L)×90 cm (W)×30 cm (H) made of Plexiglas. At the beginning of the session, each rat was placed in the center of the arena for the period of 5 min, and the following behavioral parameters were then scored: Total Distance Moved (TDM, cm); total duration for mobility (s), immobility (s); and frequency of rearing (as a measure of vertical activity) and grooming (as a measure of horizontal activity). At the end of each session, rats were removed from the open field and the experimental chamber was thoroughly cleaned with a damp cloth and dried (Shabani *et al.*, 2012a).

Statistical Analysis: Results were expressed as the mean±SEM. One way ANOVA was used for multiple comparisons followed by Turkey *post hoc* test. Unpaired t-tests were used to compare groups of sexes. Two-way ANOVAs for repeated measures were performed on body mass, motor learning, and the learning phase of the Morris water maze. $p<0.05$ was considered statistically significant. All computations were made using the SPSS software package (version 16.0).

RESULTS

Morris water maze task: The results of the training trials of the Morris Water Maze (MWM) task are depicted in Fig. 1. The imipenem-and Saline-treated groups took progressively less time to locate the hidden platform over the course of the 12 trials during the training period. The time latency ($p<0.001$) and total distance moved ($p<0.05$) at the 2nd and 3rd blocks for both the male and female imipenem-treated groups were dose dependently higher in comparison with the saline group (Fig. 1a, b). Moreover, female imipenem- treated group (40 mg kg^{-1}) showed significant lower escape latency ($p<0.05$) in comparison with the high dose imipenem treated group (Fig. 1a, b). There were no significant differences in the swimming speeds among the groups during all periods (data not shown); indicating that the swimming speed did not have influence on the latencies. In the probe test, the percentage of distance and duration travelled by imipenem-treated rats (80 mg kg^{-1}) in the correct quadrant was significantly lower ($p<0.001$) in comparison with the saline-treated groups (Fig. 1c). Moreover, results from the probe trial indicated that imipenem-treated rats (80 mg kg^{-1}) spent significantly less ($p<0.001$) time (%) and distance in the correct quadrant than the imipenem-treated rats in the lower dose (Fig. 1c). There was no significant difference between the saline and imipenem-treated groups for the crossing number to the correct quadrant. To assess for gross physical, sensory, motor, or motivational impairments, 5 rats in each group were first trained in a task with a visible escape platform. Data of visible platform train did not show any significant difference between the saline and imipenem-treated groups for the escape latency and distance moved.

Passive avoidance learning test: Figure 2 shows the effects of imipenem treatment on the mean number of shocks that rats of each group received to remain in the light compartment for 5 consecutive min. The results showed that the number of learning trials were significantly higher in male ($p<0.001$) and female ($p<0.01$) imipenem-treated groups (80 mg kg^{-1}) in comparison with the saline-treated groups (Fig. 2a). Data also shows significant differences between the two male imipenem groups ($p<0.001$).

When the testing was performed 1 days after the shock experience, the step-through latency was significantly decreased in imipenem-treated rats (male: $p<0.001$, female: $p<0.05$ for low dose and $p<0.001$ for high dose) compared to the saline groups (Fig. 2b). Moreover, the male imipenem treated groups showed lower ($p<0.05$) step through latencies in comparison with the female imipenem treated group (40 mg kg^{-1}). The

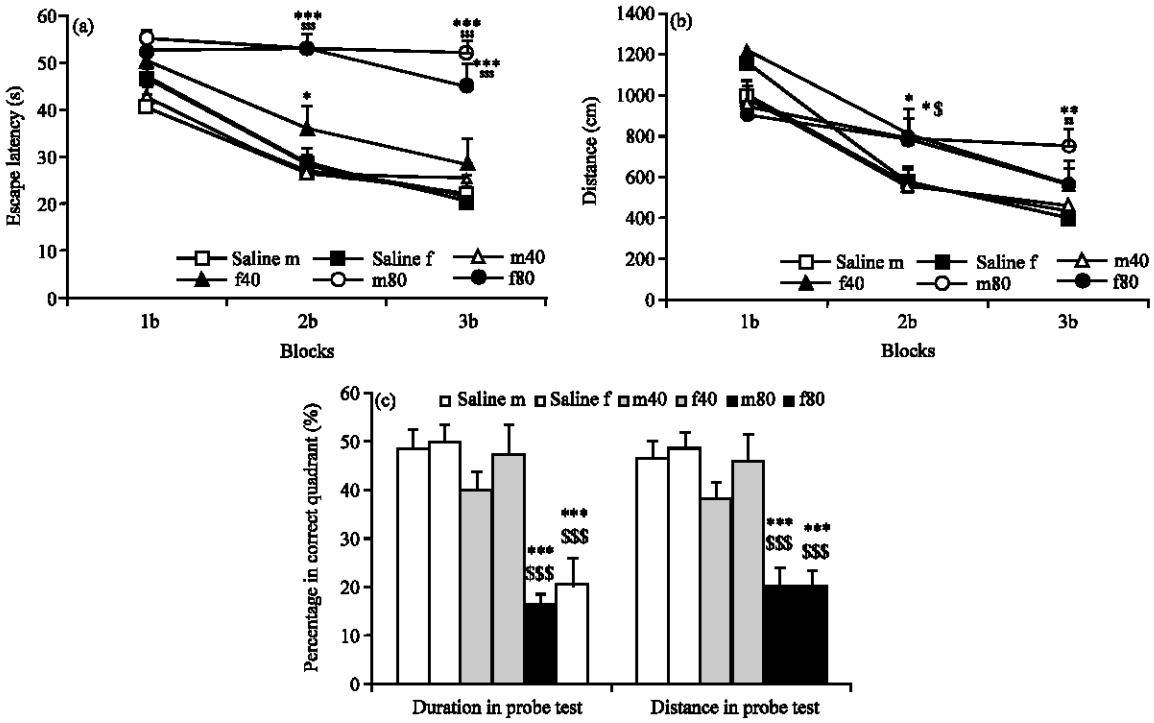

Fig. 1(a-c): Hidden platform training in the Morris water maze acquisition task across sessions following 7days of treatment with imipenem. Imipenem-treated male and female rats showed significant increases in both distance traveled (a and b) Escape latency, compared with the saline-treated rats. In the probe test and (c) The path length traveled and percent swimming time by imipenem-treated rats in the correct quadrant was significantly less than that for the saline-treated rats; *p<0.05; **p<0.01; ***p<0.001 compared with the male and female saline-treated rats; $^{\$\$\$}$p<0.001 compared with the female and male imipenem-treated rats (40 mg kg^{-1}); b1-3: Blocks 1-3; M/F: Male/female

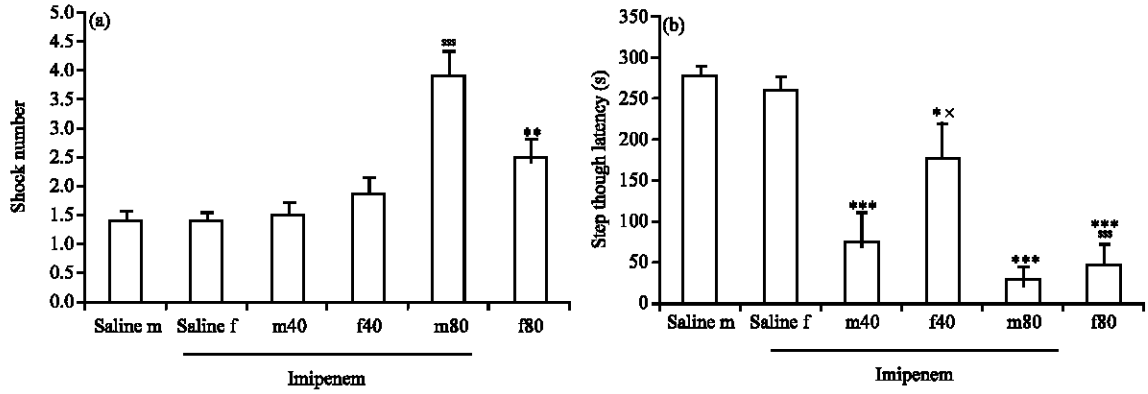

Fig. 2(a-b): (a) Effect of administration of imipenem in the passive avoidance task. Male and female imipenem rats showed significant differences in the shock number and (b) Step through latency with the saline treated group. ***p<0.001, **p<0.01, *p<0.05 compared with the male and female saline-treated group; $^{\$\$\$}$p<0.001 versus male imipenem group; $^{\$\$}$p<0.01 compared with female imipenem rats (40 mg kg^{-1}); ^{x}p<0.05 versus male imipenem rats (40 mg kg^{-1})

step-through latency in female rats at the high dose imipenem treated group was significantly decreased in comparison with the low dose (p<0.01).

Imipenem treatment did not alter the time in dark compartment (sec) and crossing number in 1 day after the shock experience (data not shown).

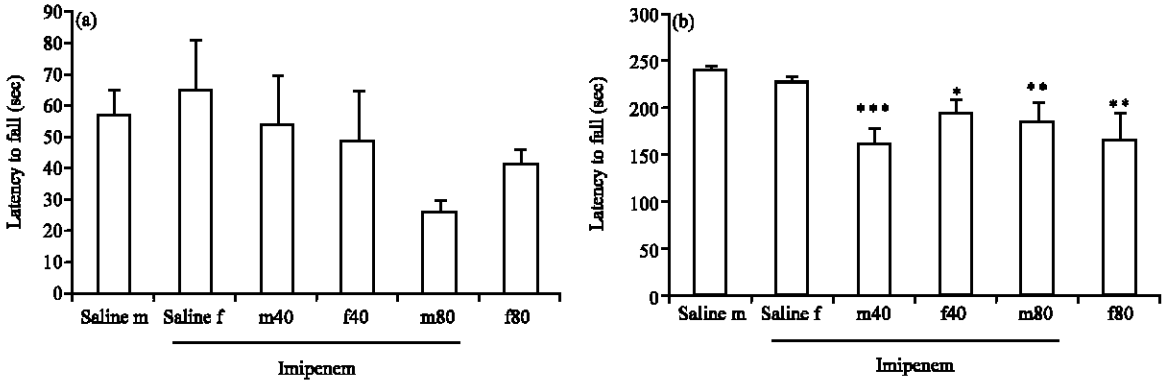

Fig. 3(a-b): (a) The effects of the imipenem on rotarod and hanging test performance. It was found that imipenem exposure profoundly alters motor function in male and female rats and (b) Imipenem treated rats significantly affected the motor coordination by rotarod performance, * $p<0.05$, ** $p<0.01$; *** $p<0.001$ for male and female imipenem-treated rats, compared with the saline groups, imipenem had no significant effect on hanging test performance

Hanging test: When muscle strength evaluations were performed by grasping test in imipenem-treated rats, data showed that imipenem treatment did not affect performance in the hanging test (Fig. 3a).

Rotarod test: Treatment with imipenem also demonstrated a deficiency in coordination on the accelerating rotarod. Imipenem exposure altered motor function in male and female rats. Rats in the imipenem-treated groups (low dose: male, $p<0,001$; female, $p<0.05$ and high dose: male and female, $p<0.05$) stayed on the accelerating rotarod for significantly shorter periods in comparison with the saline-treated groups (Fig. 3b).

Open field test: The open field test was conducted to examine locomotors activity and anxiety-related behavior. This study showed significant effects of imipenem treatment on open field results in young male and female rats in comparison with the saline-treated groups. The rearing frequency, the grooming frequency, the time spent in perimeter and the time spent in center for both male and female imipenem-treated groups were significantly different compared to the saline groups (Fig. 4). The rearing frequency was decreased ($p<0.01$) in imipenem treated groups compared to saline rats (Fig. 4a). The grooming frequency was dose dependently increased ($p<0.001$) in both male and female imipenem-treated groups in comparison with saline groups (Fig. 4b). Rats in the higher dose of female imipenem group spend more time in the center in comparison to the lower dose while there was no significant difference in the time spent in outer zone among six groups (Fig. 4c-d). However, no significant differences were observed in total distance moved, velocity, duration of mobility and immobility among the saline-and imipenem-treated groups (Fig. 4e-h).

Table 1: Effect of imipenem treatment on body weight in imipenem- and saline treated groups on the 23rd, 26th and 29th days of study

	Body weight (g)		
	23rd	26th	29th
Group	PND23	PND26	PND29
Saline M	30.0±0.8	36.0±0.5	52.4±2.4
Saline F	30.4±1.6	35.2±1.0	50.6±1.5
Imipenem M (40 mg kg^{-1})	26.6±0.3	37.2±0.4	52.0±0.5
Imipenem F (40 mg kg^{-1})	28.0±0.8	37.6±1.1	49.8±1.3
Imipenem M (80 mg kg^{-1})	31.3±0.5	34.5±0.8	41.7±1.0***
Imipenem F (80 mg kg^{-1})	30.1±0.9	27.4±0.9***	36.9±1.2***

Values represent the Mean±SEM. No differences were observed in body weight between saline-and imipenem-treated groups on the 23rd day of testing, while exposure to imipenem significantly decreased body weight in female imipenem-treated rats in the 26th, and 29th day of treatment, and for the male imipenem-treated rats in the 29th day of treatment. ***$p<0.001$ male and female imipenem-treated rats compared with saline-treated rats (n: Least 10 rats in each group, PND: Post-natal day; Saline M: Male saline-treated (control) rats, Saline F: Female saline-treated (control) rats, Imipenem M: Male imipenem-treated rats and Imipenem F: Female imipenem treated rats

Effects of exposure to imipenem on body mass: In the present study, the effect of imipenem treatment on body weight has been studied. No differences were observed in body mass between saline- and imipenem-treated groups on the 23rd day of testing. Exposure to imipenem significantly decreased body mass in female imipenem-treated rats in the 26 and 29th day of treatment ($p<0.001$), while body mass in the male imipenem-treated rats significantly decreased in the 29th day of treatment ($p<0.001$). Imipenem effects on the body mass are shown in Table 1.

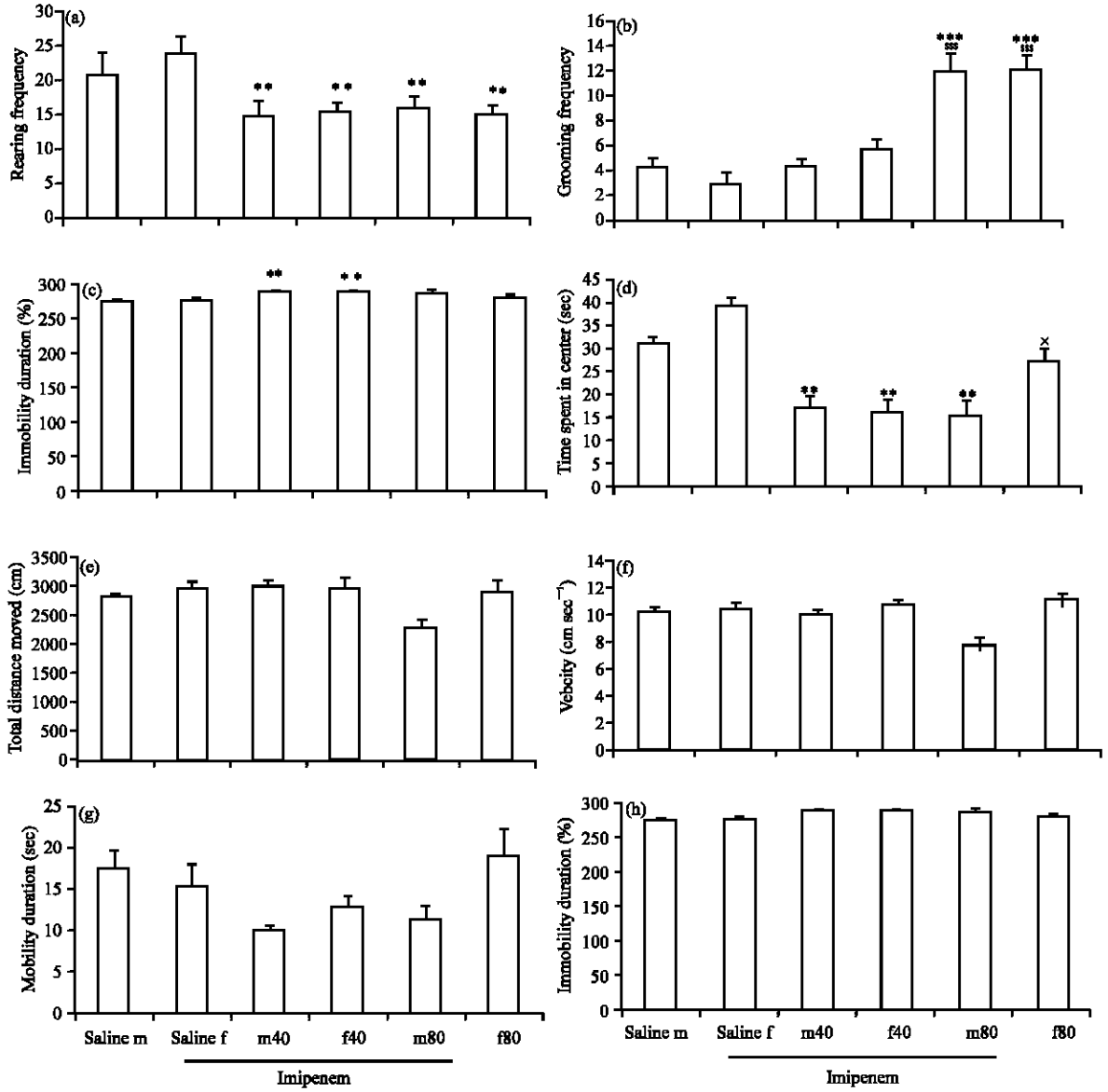

Fig. 4(a-h): The effect of imipenem on open field test performance. Imipenem treatment significantly decreased (a) Vertical rearing frequency, (b) Increased grooming frequency. Time spent in perimeter (c) Center (d) Zones significantly have been changed in male and female imipenem-treated rats during open-field trials. Imipenem had no significant effect on the total distance moved (e), Velocity (f), The mobility (g) and The immobility (H). **p<0.01; ***p<0.001; compared with the saline-treated groups; $^{\$\$\$}$p<0.001 compared with male and female imipenem rats (40 mg kg^{-1}); ^{x}p<0.05 versus male imipenem group (80 mg kg^{-1})

DISCUSSION

Beta Lactam antibiotics have been reported to have some degree of neurotoxicity and convulsive activity in experimental animals as well as in clinical situations (Norrby, 1996; Spapen *et al*., 2011; Sunagawa and Nouda, 1996; De Sarro *et al*.,1989). Imipenem/cilastatin as a Beta Lactam antibiotic has been reported to induce seizures in humans at clinical doses (Semel and Allen, 1991), but there aren't obvious evidences about other possible neurotoxic effect of this drug, such as its effect on motor and memory systems. The findings of this study provide new evidences that exposure to the antibiotic compound imipenem induces stout alterations in motor function and exploratory activity and also causes impairment in spatial and passive avoidance learning and memory.

The motor activity and exploratory behaviors of rats in both sexes were dramatically affected by exposure with imipenem. Imipenem groups displayed disruptions in their spatial and passive avoidance learning and memory when compared to saline groups. The time required for spatial acquisition and superior probe trial performance was increased. Besides, a shorter distance swam by the saline groups also suggested disruption of learning and memory in the imipenem groups. However, in the present study, Present data showed that imipenem have some destructive effects on motor and cognition related region in central nervous system. Previous studies has suggested that the neurotoxic effects of these antibiotics may be related to their abilities to inhibit γ-Amino Butyric Acid (GABA) receptor binding (Day *et al*., 1995; Jin *et al*., 1999). Imipenem did not induce convulsions at doses 40 and 80 mg kg^{-1}; therefore, it could be consider that the dose of the imipenem used in the present study may not be enough to induce convulsions effect in this situation.

The â-lactams have been shown to have stronger effects on CNS than other classes of antibiotics, (Chow *et al*., 2004; Hantson *et al*., 1999) The neurotoxic effects of carbapenem, consist confusion, psychosis, myoclonus, and seizures (Akisue *et al*., 1998; Chow *et al*., 2004; Dupuis *et al*., 2001; Sunagawa *et al*., 1995). But their neurotoxic effects on motor function and memory are less recognized. It has been reported that mechanisms involved in imipenem convulsant action, are decreasing of inhibition (De Sarro *et al*. 1995; Williams *et al*., 1988) and increasing of excitation (De Sarro *et al*. 1995). The neurotoxicity induced by a carbapenem drug may relate to increased vulnerability of neurons to physiological glutamate concentrations, resulting in oxidative stress and disruption of mitochondrial energy metabolism (Tune *et al*., 1989).

The cortex and cerebellum, which are involved in motor coordination and learning of new motor skills, could be one of the brain regions most vulnerable to exposure to carbapenem drugs. It is also suggested that neuronal networks in the cortex are involved in imipenem/cilastatin-induced seizures (Zivanovic *et al*., 2004b). $GABA_A$ is present in the cortex and the pyramidal neurons receive a high density of GABAergic fibers. These neurons are presumed to be highly involved in the adverse effect of â-lactams (Fujimoto *et al*., 1995). B-lactam antibiotics as well as imipenem suppress the IGABA (GABA-induce inward Cl-current) not only by a channel-blockade but also by interaction with the $GABA_A$ receptor sites (Fujimoto *et al*., 1995). Moreover, recent studies showed that the excitatory neurotransmission could generate and/or propagate the imipenem/cilastatin-induced seizures in rats (Zivanovic *et al*., 2004a).

The cerebellum and hippocampus are potential targets for the deleterious effects of drugs including imipenem. On the other hand, there is sufficient evidence to suggest that imipenem has the ability to cross the Blood-Brain-Barrier (BBB) (Akisue *et al*., 1998; Sunagawa *et al*., 1995), and therefore, probably can affect on cognition. The limbic system, which seems, support a variety of functions including emotion, behavior, motivation, long-term memory, and olfaction (Lalonde *et al*., 2002) is the model for human limbic seizures caused by imipenem/Cilastatin (Zivanovic *et al*., 2004c).

In this study the relationship between sex and consequent behavior deficits, in rats after imipenem administration has been also examined. In the rat IP or IV injection studies, imipenem/cilastatin produced some behavioral changes (Mallalieu *et al*., 2009; Volchegorskii and Trenina, 2006), whereas less sex differences were observed. In the present study, female rats spent more time in the central area of the open field apparatus in comparison with male rats. Since, it could be concluded that female rats were less anxious than males. Furthermore female rats showed higher escape through latencies in passive avoidance memory compared to the male rats. It is difficult to conclude with certainty the causes of the observed sex differences in present findings. However, it can be proposed that these differences may be related to sexual dimorphism in the brain organization and function. There are evidences of sex differences in many aspects of brain structure, neurotransmitter systems, and neuroendocrine regulation (Allen *et al*., 2003; Tune *et al*., 1989). Further studies are required to fully elucidate the emotional state of the experimental subjects following imipenem treatment and also to identify the nervous pathways involved in these observations.

CONCLUSION

It can be concluded that animals treated with imipenem suffer from motor activity and cognitive impairment. Furthermore, exposure to imipenem causes impairment in spatial and passive avoidance learning and memory. Hippocampal and cerebellum functions, including learning, memory, and motor function of male and female rats were not differentially affected by exposure to imipenem, which suggests this impairment is less affected by sex differences. However, female animals treated with imipenem were less anxious.

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CONFLICT OF INTEREST

The authors declare no conflict of interest and declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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