Gabapentin, A GABA analogue, enhances cognitive performance in mice

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Gabapentin is one of the new antiepileptic drugs (AEDs) launched recently. The advantage of new AEDs includes newer mechanism of action, broad spectrum of antiseizure effects, lesser drug interactions and fewer side effects. Gabapentin (GBP) a GABA analogue, is efficacious in several neurological and psychiatric conditions and it is conventionally used in the treatment of partial epilepsies. In this study, we aimed to evaluate the effects of GBP on learning and memory processes of naive mice in Morris water maze (MWM), passive avoidance (PA) and modified elevated plus maze (mEPM) tests. GBP (5 and 10 mg/kg, i.p.) was administered on the probe trial of MWM and on the acquisition session of PA and mEPM tests. In the MWM test, GBP (10 mg/kg) significantly increased the time spent in target quadrant and GBP (5 and 10 mg/kg) significantly decreased the distance to platform compared to control group. In the mEPM test, GBP (5 and 10 mg/kg) significantly decreased the transfer latency compared to control group on the second day and in the PA test, GBP (5 and 10 mg/kg) significantly prolonged retention latency compared to control group. Our results indicate that GBP has improving effects on spatial and emotional cognitive performance of naive mice in MWM, PA and mEPM tasks.

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genesis in rats were investigated and the results showed that lamotrigine did not produce any change in cognitive function, while carbamazepine produced cognitive dysfunction [2].

There are few systematic data on the effects of GBP on specific cognitive domains. Although preliminary results are promising with GBP for its effect on memory storage, the effects of GBP still remain to be explored on spatial and emotional learning and memory functions in mice. The aim of this study was to investigate the effects of GBP on spatial and avoidance cognitive performance in Morris water maze (MWM), passive avoidance (PA) and modified elevated plus maze (mEPM) tasks in naive mice.

GBP was purchased from Sigma Chemical Company (Sigma, St. Louis, MO) and dissolved in saline. GBP was freshly prepared and administered by intraperitoneal (i.p.) route in a volume of 1 ml per 10 g body weight of mice. Control groups received the same volume of vehicle. Doses that do not affect locomotor activity of animals were selected and previous literature taken into consideration [1]. GBP was administered intraperitoneally (i.p.) 30 min before the tests.

Male BALB/c mice (Istanbul University Research Center, DETAM, Turkey) weighing 35–45 g were housed five–six per home cages (L 30 × W 20 × h 12.5 cm) in an animal colony facility for 2 weeks before the start of the experiment. The animals were maintained in constant room temperature (22 ± 2 °C) under a 12-h light/dark cycle (light onset at 07:00 h). Tap water and food pellets were provided ad libitum. All animals were naive to tests. Each mouse was tested individually and only once. Experiments were conducted between 10:00 and 14:00 h. All procedures were in compliance with the European Community Council Directive of 24 November 1986 and ethical approval was granted by the Ethics Committee of Kocaeli University. (Number: KOU/HADYEK-6/1-13, Kocaeli, Turkey).

MWM was a circular pool (90 cm diameter and 30 cm height) that was filled to a depth of 14 cm with water (22 ± 1 °C) and rendered opaque by the addition of small black balls. The pool was located in a semi-soundproof, dimmed test room illuminated with a table lamp (80 lux), a number of extra-maze visual cues, including a white-black-colored poster on the wall, a camera and the experimenter. Maze was divided into four quadrants, and three equally spaced points were used as starting positions around the edge of the pool. The order of release positions varied systematically throughout the experiment. An escape platform (6 cm diameter and 12 cm height) was located in one quadrant 1 cm above the water surface during the familiarization session and 1 cm below the water surface during other sessions. Videotracking conducted with a video camera focused on the full diameter of the pool. Navigation parameters were analyzed using the ETHOVISION 3.1 video analysis system (Noldus). Mice were trained during five daily sessions (S1, S2, S3, S4, S5). One familiarization and four acquisition sessions were performed. During familiarization session and acquisition phase, each mouse was given three trials. Delay between trials was 60 s, and a 2-day interval was used between sessions. For each daily trial, mice was taken from the home cage and placed into the maze at one of three randomly determined locations with its head facing the center of maze. After the mouse had found and climbed on to the platform, trial was stopped and escape latency was recorded. If the mouse had not climbed onto the platform in 60 s, the trial ended automatically and the experimenter guided the mouse to the platform and an escape latency of 60 s was recorded [6]. Twenty-four hours after the last acquisition session, a probe trial was used to assess the mouse spatial retention of the location of the hidden platform. During this trial, platform was removed from the maze and the mouse was allowed to search the pool for 60 s. The percent of time spent in each quadrant was recorded.

Distance to platform and time spent in escape platforms quadrant analyses were used as measures to determine spatial memory, whereas the swim speed parameter was used to assess locomotor function.

Experiments were conducted in a dimly lit, semi-soundproof room, illuminated with table lamp (80 lux). Transfer latency was used as an index of learning and memory [17]. Maze was made of wood and consisted of two open (29 cm long × 5 cm wide) and closed arms (29 cm × 5 cm with 15 cm high walls) forming a square cross with a 5 cm square center piece. In order to avoid falls the open arms was surrounded by a short (1 cm) plexiglass edge. The maze was elevated 40 cm above the floor. The open arms and central platform were painted white and enclosed arms were painted black. The animals were randomly assigned to different experimental and control groups. In the acquisition session (on day 1), each mice was gently placed at the distal end of an open arm of the apparatus facing away from central platform. The time it took for the mice to move from the open arm to either of the enclosed arms (transfer latency) was recorded. Training (repeated exposure of animal to open arms) shortens this parameter, possibly as a consequence of learning acquisition and retention. If the mice did not enter the enclosed arm within 90 s, it was excluded from further experimentation. The criterion of an animal’s entry into the enclosed arm was crossing with all four legs of an imaginary line separating the enclosed arm from the central space. After entering the enclosed arm, the mice was allowed to move freely in the maze regardless of open and enclosed arms for 10 s. Then, the mice was returned to its home cage. Retention session followed 24 h after the acquisition session (on day 2). The mice were put into the open arm and the transfer latency was recorded again.

Animals were trained in a one-trial, step-through, PA apparatus for evaluating memory based on contextual fear conditioning and instrumental learning [15]. Decrease in retention latency indicates an impairment in memory in the PA task. The apparatus consisted of a box with an illuminated part (L 7.125 × h 14 cm) and a dark part (L 24 × h 14 cm), both equipped with a grid floor composed of steel bars (0.3 cm diameter) spaced 0.9 cm apart. The inhibitory avoidance task consisted of two trials. On the first day of training, mice were placed individually into the light compartment and allowed to explore the boxes. The intercompartment door was opened after a 60-s acclimation period. In the acquisition trial, each mouse was placed in the illuminated compartment, which was lighted by a bright bulb (2000 lux). The animals received drugs prior to acquisition training.

If the mouse stepped into the dark compartment (2/3 of the tail in the dark compartment), the door was closed by the experimenter and an inescapable foot shock (0.25 mA/1 s) was delivered through the grid floor of the dark compartment. A cutoff time of 5 min was selected. The time taken to enter the dark compartment (training latency) was recorded. Immediately after the shock, the mouse was returned back to the home cage.

The retention trial started 24 h after the end of the acquisition trial. Each mouse was placed in the illuminated compartment as in the training trial. The door was opened after a 30-s acclimation period. The step-through latency in the retention trial (with a maximum 300 s cutoff time) was used as the index of retention of the learned experience. Shock was not applied at the retention trial.

One-way analysis of variance (ANOVA) post-hoc Tukey test was used to analyse PA and MWM tests data. Wilcoxon t-test (first day vs. second) and Kruskal–Wallis ANOVA followed by Dunns test (vs. control group on second day) were preferred for the analyses of mEPM test. Data are expressed as the mean values ±SEM. p < 0.05 accepted as statistically significant.

GBP (5 mg/kg) had no effect on the time spent in target quadrant. GBP (10 mg/kg) increased the time spent in target quadrant compared to control (n = 9–10, p < 0.01 vs. control group ANOVA posthoc Tukey, F(2, 28) = 7.26, p = 0.0031) (Fig. 1a).
GBP (5, 10 mg/kg) administration decreased the distance to platform compared to control (\(n = 9–10, p < 0.001\) (vs. control) ANOVA posthoc Tukey, \(F(2, 28) = 49.33, p < 0.0001\)) (Fig. 1b).

GBP (5, 10 mg/kg) did not affect the swim speed in MWM test compared to control (\(n = 9–10\), ANOVA posthoc Tukey, \(F(2, 28) = 1.8, p = 0.18\)) (Fig. 1c).

Mean TL of GBP (5, 10 mg/kg, i.p.) or vehicle (on first day and second day), given 30 min before acquisition session in the mEPM in mice are presented in Fig. 2.

GBP had no effect on the TL on the first day (TL1) compared to that of the vehicle treated group (\(n = 8–10\), KW = 5.02, \(p = 0.08\), Kruskal–Wallis followed by Dunns test). 2 days TL significantly decreased compared to 1 day TL within control and GBP groups indicating that the mice remembered the presence of the enclosed arms in mEPM \(n = 8–10, p < 0.001\) (first day vs. second day, Wilcoxon \(t\)-test). On the 2nd day, GBP significantly decreased the TL2, \(p < 0.01, p < 0.001\) (vs. control on the second day), Kruskal–Wallis ANOVA followed by Dunns test, \(KW = 17.79, p = 0.0001\).

Fig. 3a shows the effect of GBP (5, 10 mg/kg, i.p.) on the first day latency (STL) of mice in PA task. GBP did not affected first day latency on training session of PA task (\(n = 9–10, F(2, 27) = 0.81, p = 0.45\), ANOVA followed by post-hoc Tukey test)

Fig. 3b shows the effect of GBP (5, 10 mg/kg, i.p.) on the retention latency during retention test of PA task. GBP significantly increased the retention latency (sec) on 2nd day compared to control and GBP (10 mg/kg) significantly increased the retention latency (sec).
Regarding different types of memory improvement by GBP [1,3,4], improving actions of GBP [4]. It is already known that, AEDs cholinergic mechanism has a possible involvement in memory not influenced by neostigmine; suggested that central muscarinic ethonium prevented the effects of posttraining GBP) and were atropine (neither methylatropine nor mecamylamine, or hexamethonium performance. In that study, these effects were prevented by ways of memories and retention performance obtained in PA task. Affective cognition by suppressing neuronal excitability or enhancing inhibition neurotransmission [16]. GBP is a cyclized analogue of GABA but it does not interact with GABA receptors, nor does it inhibit GABA uptake or prevent the degradation of GABA. However, in vivo, GBP increases the GABA accumulation in the rat brain [10]. The exact mechanism of GBP action still remains to be investigated, but its therapeutic action on neuropathic pain is thought to involve voltage-gated N-type calcium ion channels. It is thought to bind to the α2 β6 subunit of the voltage-dependent calcium channel in the central nervous system. The receptor profile is known as the direct blockade of subunits of voltage gated calcium channels and leads to reduction of release of multiple neurotransmitters [8].

GBP treatment alters the metabolism or concentration of glutamate, glycine or GABA in brain tissues. Also interact with the alpha2 delta auxiliary subunit of voltage gated calcium channels. GBP may modulate certain types of calcium currents [22] and apart from all these knowledge studies should be performed in order to clarify by which pharmacological mechanism does GBP use among these while affecting different types of cognitive performance in naive and epileptic animals.

Cognitive functions in individuals with epilepsy may be influenced by several factors among which underlying pathology, seizure type, and the detrimental effects of AEDs are most important. Therefore, in this regard, the importance of our study is that we try to evaluate the effects GBP on spatial and emotional learning and memory in non-epileptic (naive) mice which is independent of the disease or epilepsy itself.

In conclusion GBP enhances cognitive performance in MWM, mEPM and PA tasks in naive mice. Further studies should be performed to investigate the effects of chronic GBP treatment and compare GBP with at least one conventional antiepileptic drug in the same tasks both in naive animals and in epilepsy-models.

References