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Welcome to the Int J Cancer and Biomedical Research (IJCBR)**!**

It is with great pleasure that I write this editorial to welcome you to the IJCBR. This journal provides a platform for publication of original and reviews research articles, short communications, letter to editor, thesis abstract, conference report, and case studies. These types of publication are directed at the interface of the fields of cancer and biomedical research.

The IJCBR relies on a distinguished expert of the Advisory and Editorial Board Members from the top international league covering in depth the related topics. They timely review all manuscripts and maintain highest standards of quality and scientific methodology and ethical concepts. Meanwhile, we take all possible means to keep the time of the publication process as short as possible.

I take this chance to welcome your contributions to the IJCBR and have every expectation that it will soon become one of the most respected journals in both the fields of cancer and biomedical research.

Mohamed L. Salem,

Editor in Chief

INTERNATIONAL JOURNAL OF CANCER AND BIOMEDICAL RESEARCH (IJCBR)

RESEARCH ARTICLE

Lamotrigine and gabapentin ameliorate neurotoxicity induced by lipopolysaccharide in mice

Nageh A. El-Mahdy, Sally E. Abu-Risha and Fatma T. Al-Hosiny

Department of Pharmacology & Toxicology, Faculty of Pharmacy, Tanta University, Tanta, Egypt

ABSTRACT

Background: Alzheimer's disease (AD), the most common cause for dementia, is an irreversible progressive neurodegenerative disorder. **Aim:** To investigate the potential protective role of Lamotrigine (LTG) and Gabapentin (GBP) either alone and in combination in Lipopolysaccride-induced Alzheimer's disease (AD) in mice. **Materials and Methods:** Mice were divided into 5 groups: Normal control group, Lipopolysaccride (LPS) group (animals were injected by single I.P. dose of LPS in a dose of 0.8 mg/kg), LTG group (animals were injected by single I.P. dose of LPS 0.8 mg/kg and received oral LTG 30 mg/kg/day), GBP group (animals were injected by single I.P. dose of LPS 0.8 mg/kg and received oral GBP 200 mg/kg/day) and LTG+GBP group (animals were injected by single I.P. dose of LPS 0.8 mg/kg and received both oral LTG 30 mg/kg/day and GBP 200 mg/kg/day), therapy started 2-h after LPS injection for 7 successive days. Novel object recognition and Y-maze tests were conducted. Brain homogenate used for the estimation of superoxide dismutase (SOD), acetylcholine esterase (AchE) activity, glutamate, reduced glutathione (GSH) and malonyialdehyde (MDA) contents. **Results:** LPS significantly induced neurobehavioral disturbances compared to normal control with significantly higher MDA, AchE and glutamate contents, with a reduction in SOD and GSH levels. Treatment with either LTG or GBP significantly ameliorated the effects of LPS injection on neurobehavioral tests, oxidative milieu with a significant reduction in AchE activity and glutamate content in favor of LTG. Combined therapy significantly improved both neurobehavioral testing and the estimated biochemical markers. **Conclusion:** GBP and/or LTG therapy improved neurobehavioral testing in LPS-induced AD in mice by restoring oxidant/antioxidant milieu with a concomitant reduction in AchE activity and glutamate content. Furthermore; the combination of both drugs resulted in significant improvement than either one of them alone that merits further clinical investigation.

Keywords: Acetylcholine esterase; Alzheimer's disease; Gabapentin; Glutamate; Lamotrigine; Oxidative stress

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Correspondence to:
Dr. Fatma T. Al-Hosiny
Department of Pharmacology & Toxicology,
Faculty of Pharmacy, Tanta University,
Tanta, Egypt
Tel: +20403336007/409, Fax: +20403335466
Email: fatmaal.hosiny.pf.2019@gmail.com

INTRODUCTION

Alzheimer's disease (AD) is a neurodegenerative disorder, with extremely complicated pathogenesis (Yang et al., 2019) and is characterized by dementia, excessive acetyl cholinesterase (AChE) activity, the formation of neurotoxic amyloid plaque, and the aggregation of tau protein (Rasool et al., 2018).

Amyloid plaques are mainly composed of an amyloid-β peptide (Aβ) derived from amyloid precursor protein via β- and ɣ-secretases (Masters & Selkoe, 2012). These Aβ peptides polymerize into insoluble nano-filaments that accumulate in senile plaques and walls of cerebral blood vessels (Al-Hilaly et al., 2017). The neurofibrillary tangles are abnormal aggregates that mainly consist of hyper-phosphorylated microtubule-associated protein (tau protein) (Nishikawa et al., 2016) that aggregates into insoluble intra-neuronal filaments which is a major characteristic of AD (Falcon et al., 2018).

In the clinical setting, AD passes three phases; the long preclinical phase which is followed by mild impairment in cognition and lastly AD becomes clinically manifest (Parnetti et al.,

2019). Subjective cognitive deterioration in cognitively unimpaired older individuals was considered as an early clinical at-risk state for AD/dementia (Wolfsgruber et al., 2019). Agitation is a common symptom of AD with an overall prevalence of 44.6% and 61.3% among patients diagnosed with staged AD/dementia (Halpern et al., 2019).

Cognitive rehabilitation aids people diagnosed with early-stage dementia to improve their everyday functioning (Clare et al., 2019). Controlled release, targetability, and synergistic multi-channel treatment are the main factors that influence the success of AD drugs (Sun et al., 2019).

Gabapentin (GBP), a GABA analogue that increases brain synaptic GABA, decreases calcium ions influx into the neurons via a specific subunit of voltage-dependent calcium channels and may also affect glutamate (Glu) production (Meyerhoff et al., 2018). Lamotrigine (LTG) is a second-generation AED with a broad activity span, a satisfactory side-effect profile, simpler dosing than earlier drugs and better efficacy in diverse epilepsy syndromes (Yasam et al., 2016). Unfortunately, LTG, is the most interacting drug of the new AED and its metabolism is susceptible to both enzyme inhibition and induction (Johannessen Landmark & Patsalos, 2010). However, the beneficial effects of the new generation of AED as GBP and LTG dominate over mitochondrial toxic effects (Finsterer & Scorza, 2017). This study aimed to explore the potential protective role of Lamotrigine and Gabapentin either alone and in combination in LPS-induced Alzheimer's disease (AD) in mice.

MATERIALS & METHODS

Animals

The study comprised 80 male albino mice (25 gm). Mice were purchased from the laboratories of the Ministry of Agriculture and kept under standard conditions, temperature 20^{o}C, humidity 60% and 12-hs day/night cycle and maintained on a standard diet and free access to water till the start of the study. The experimental work described in this study complies with guidelines for the care and use of laboratory animals and the ethical principles adopted by the “Research Ethics Committee”, Faculty of Pharmacy, Tanta University (PT00015).

Induction of neuroinflammation and amyloidogenesis

LPS (a single I.P. injection of LPS (0.8 mg/kg) dissolved in 1 % Tween 80 solution in normal saline) was used for inducing brain neuro-inflammation and amyloidogenesis, in a simulation to AD, according to (Khairallah et al., 2016).

Experimental design

Animals were divided randomly into five groups (16 mice in each group): Normal control group (naïve group), Positive control group: animals and were injected IP by LPS (single dose of 0.8 mg/kg), but received no drugs, LTG group: injected by LPS and received oral LTG 30 mg/kg/day (Wang et al., 2016) starting 2-h after LPS injection for 7 successive days, GBP group: injected by LPS and received oral GBP 200 mg/kg/day (Rizwan et al., 2003) starting 2-h after LPS injection for 7 successive days and combination group: injected by LPS and received both oral lamotrigine (30 mg/kg/day) and gabapentin (200 mg/kg/day) starting 2-h after LPS injection for 7 consecutive days. LTG and GBP were suspended in 0.5%carboxy methyl cellulose (CMC).

Design for behavioral testing

The day of induction was considered as test day-1. On day-7, animals were trained for behavioral tests. On the next day, behavioral studies were performed and included Y-maze test and novel object recognition (NOR) test to evaluate the spatial and non-spatial memory, respectively.

The Y-Maze Task test

Y-Maze Task test was performed according to (Sarter et al., 1988; Maurice et al., 1994) to assess the spontaneous alternation behavior which is considered as a measure of the working memory. The mean number of alternations was listed for each group. Alternation was defined as the total number of individual arm entries into all of the three arms divided by the maximum possible alternations.

Novel object recognition (NOR) Task

NOR was estimated according to (Ennaceur, 2010). This test is conducted to evaluate the capability of mice to recognize a novel object in their environment. RI is defined as the time that was spent exploring the novel object to the total time spent exploring both objects during the test phase, i.e., $RI = T_N / (T_{familiar} + T_{novel})$.

Laboratory investigations
Sampling

Animals of all groups were anesthetized by light ether and sacrificed by decapitation, 24-hr after receiving the last dose of drugs. Brains were rapidly removed on ice-cold saline. Part of the brain was used for histopathological examination. The other part of the brain was homogenized in cold saline using a tissue homogenizer (yellow line, DI18 basic, Germany) and centrifuged at 4000 rpm at 4°C for 15 min using a cooling centrifuge (Sigma 3-30 k USA), the supernatant was withdrawn and kept at -80°C till be assayed.

Investigations

1. ELISA estimation of brain tissue content of
   - Superoxide dismutase (SOD) activity level using a quantitative sandwich ELISA kit for mouse SOD and provided by MyBiosource.com (Southern California, San Diego, USA) (Robak & Gryglewski, 1988).
   - Acetylcholine esterase (AchE) activity level using a quantitative sandwich ELISA kit for mouse AchE and provided by Cusabio Technology LLC (Houston, Texas, USA) (Ellman et al., 1961).
   - Glutamate (Glu) level using quantitative ELISA kit for mouse glutamate and provided by MyBiosource.com (Southern California, San Diego, USA) (Lee et al., 2002).
2. Colorimetric estimation of brain content of GSH (Ellman, 1959) and MDA (Ohkawa et al., 1979).

Histopathology

Brain tissues were fixed in 10% neutral buffered formalin (pH 7.4) for 72 h, washed, dehydrated, embedded in paraffin wax and sectioned serially with a microtome at 3 µm thickness. They were all stained with hematoxylin and eosin (H&E) for histopathological investigation.

Statistical analysis

Results are presented as mean and standard deviation. Comparison of data groups was carried out using one-way analysis of variance (ANOVA) followed by Tukey, multiple comparison tests. IBM SPSS (Version 23, 2015) for Windows statistical package was used for statistical analysis. P-value <0.05 was considered statistically significant.

RESULTS

Effect of different treatments on neurobehavioral testing of animal groups

LPS administration showed deterioration on neurobehavioral testing compared to animals of the normal control group. Regarding drug therapy, treated animals with either LTG or GBP have shown significant improvement in neurobehavioral testing versus untreated animals. However, animals that received drug combination showed significantly higher scores on Y-maze test (Figure 1), while showed non-significantly higher results of NOR task testing compared to animals that received a single drug (Table 1, Figure 2).

Effect of different treatments on biochemical parameters of animal groups

Mean brain tissue activity of SOD (Table 2, Figure 3) and GSH (Table 2, Figure 4) were significantly lower in LPS group compared to the normal control group. Treated animals with either LTG or GBP significantly increased SOD and GSH contents as compared to LPS group. Moreover, drug combination significantly preserved activity levels of these enzymes compared to a single-drug therapy with a significant difference in favor of LTG group. Subsequently, mean MDA contents (Table 2, Figure 5) were significantly higher in brain tissue of LPS group compared to normal control group. Treatment with either LTG or GBP significantly decreased MDA contents as compared to LPS group. Also, drug combination significantly reduced MDA contents compared to single-drug therapy with a significant difference in favor of LTG group. Brain tissue contents of AchE (Table 2, Figure 6) and glutamate (Table 2, Figure 7) showed significant changes between LPS group.

Table 1. Effect of different treatments on neurobehavioral testing of animal groups

Groups	Normal neuronal cells	Congestion and perivascular oedema	Neuronal injury	Gliosis	Extent of lesions
Control	++++	-	-	-	-
LPS	++	+++	+++	+++	+++
GBP	+++	+	++	+	+
LTG	+++	+	+	+	+
GBP+LTG	+++	++	++	+	+

Data are presented as mean±SD; a: significant difference versus the control group (P1); b: significant difference versus LPS group (P2); c: significant difference versus LTG group (P3); d: significant difference versus GBP (P4); P<0.05 indicates significant difference.

Table 2. Mean contents of SOD, GSH and MDA estimated in brain tissue of animals of studied groups

Group Test	Control	LPS	LTG	GBP	LTG + GBP
SOD (U/g tissue)	31.24±2.24	4.88±1.23[a]	15.54±1.08[ab]	10.72±0.81[ab]	21.85±1.27[abcd]
					(P1)<0.0001
					(P2)<0.0001
			(P1)<0.0001	(P1)<0.0001	(P3)<0.0001
		(P1)<0.0001	(P2)<0.0001	(P2)<0.0001	(P4)<0.0001
GSH (nmol/g tissue)	24.83±1.64	4.23±0.59[a]	12.69±1.21[ab]	8.34±1.27[ab]	17.77±1.7[abcd]
					(P1)<0.0001
					(P2)<0.0001
			(P1)<0.0001	(P1)<0.0001	(P3)<0.0001
		(P1)<0.0001	(P2)<0.0001	(P2)<0.0001	(P4)<0.0001
MDA (nmol/g tissue)	1.87±0.23	14.05±0.86[a]	6.7±0.42[ab]	9.44±0.52[ab]	4±0.19[ab]
			(P1)<0.0001	(P1)<0.0001	(P1)<0.0001
		(P1)<0.0001	(P2)<0.0001	(P2)<0.0001	(P2)<0.0001
AchE (mU/g tissue)	1.49±0.14	5.32±0.37[a]	2.66±0.15[ab]	3.34±0.14[ab]	2.14±0.07[abcd]
					(P1)<0.0001
					(P2)<0.0001
			(P1)<0.0001	(P1)<0.0001	(P3)<0.0001
		(P1)<0.0001	(P2)<0.0001	(P2)<0.0001	(P4)<0.0001
Glutamate (mmol/g tissue)	1.39±0.14	5.49±0.4[a]	2.56±0.14[ab]	3.39±0.16[ab]	2.07±0.07[abcd]
					(P1)<0.0001
					(P2)<0.0001
			(P1)<0.0001	(P1)<0.0001	(P3)=0.0005
		(P1)<0.0001	(P2)<0.0001	(P2)<0.0001	(P4)<0.0001

Data are presented as mean±SD; a: significant difference versus the control group(P1); b: significant difference versus LPS group(P2); c: significant difference versus LTG group(P3); d: significant difference versus GBP(P4); P<0.05 indicates significant difference.

Table 3. Semiquantitative scoring of the histopathological findings within the different groups (-) indicates normal tissue, + indicates mild lesions, ++ indicates moderate lesions, + indicates severe lesions and ++++ indicates severe diffuse lesions

Group Test		Control	LPS	LTG	GBP	LTG + GBP
RI	Score	0.89±0.05	0.34±0.04[a]	0.62±0.12[ab]	0.56±0.14[ab]	0.64±0.12[ab]
				(P1)<0.0001	(P1)<0.0001	(P1)=0.0002
			(P1)<0.0001	(P2)<0.0001	(P2)=0.0013	(P2)<0.0001
SAB (%)	Score	69.04±7	15.54±4.27[a]	39.96±6.7[ab]	35.52±7.65[ab]	51.06±12.68 [abcd]
						(P1)=0.0008
						(P2)<0.0001
				(P1)<0.0001	(P1)<0.0001	(P3)=0.0700
			(P1)<0.0001	(P2)<0.0001	(P2)=0.0002	(P4)=0.0045

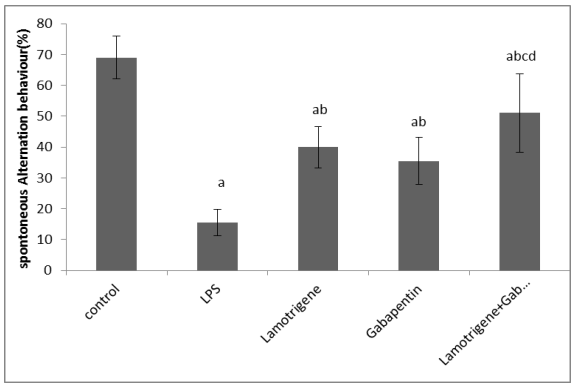

Figure 1. Effect of different treatments on Y-maze test. Data shown are mean ± SD (n = 8 mice/group). Value significantly different vs (a) normal control or (b) LPS or (c) LTG or (d) GBP ($p < 0.05$).

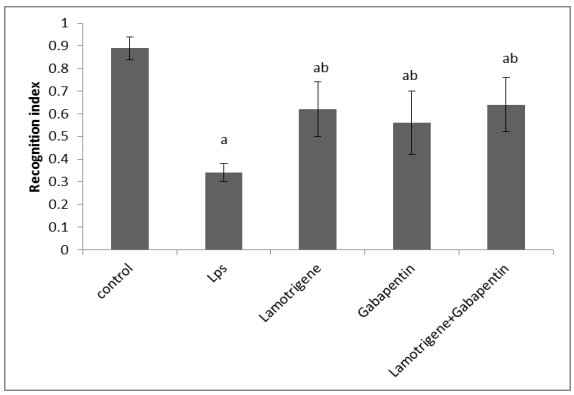

Figure 2. Effect of different treatments on NOR task testing. Data shown are mean ± SD (n = 8 mice/group). Value significantly different vs (a) normal control or (b) LPS ($p < 0.05$).

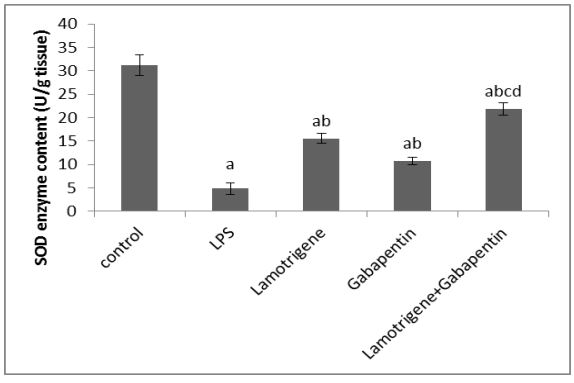

Figure 3. Effect of different treatments on superoxide dismutase (SOD) enzyme content. Data shown are mean ± SD (n = 8 mice/group). Value significantly different versus (a) normal control or (b) LPS or (c) LTG or (d) GBP ($p < 0.05$).

and the control group. Treatment with either LTG or GBP significantly decreased AchE and glutamate contents as compared to LPS group. Drug combination did favorably than single drug as shown by the significantly lower contents of

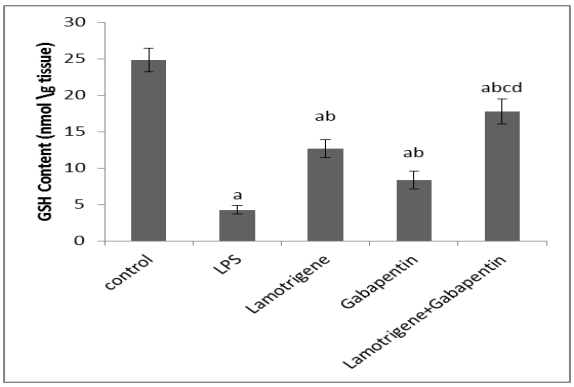

Figure 4. Effect of different treatments on glutathione (GSH) content. Data shown are mean ± SD (n = 8 mice/group). Value significantly different versus (a) normal control or (b) LPS or (c) LTG or (d) GBP ($p < 0.05$).

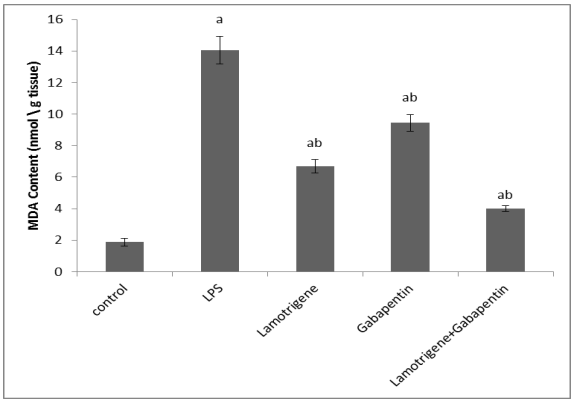

Figure 5. Effect of different treatments on malondialdehyde (MDA) content. Data shown are mean ± SD (n = 8 mice/group). Value significantly different versus (a) normal control or (b) LPS or (c) LTG or (d) GBP ($p < 0.05$).

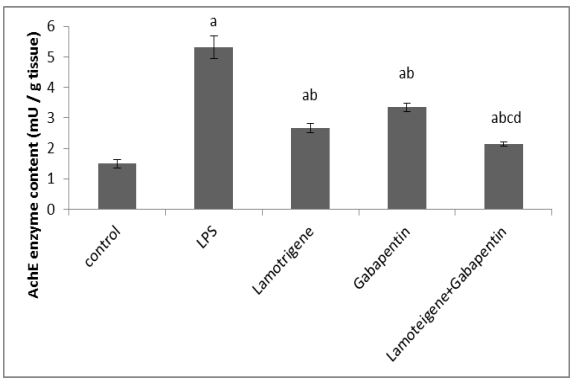

Figure 6. Effect of different treatments on acetylcholine esterase (AchE) content. Data shown are mean ± SD (n = 8 mice/group). Value significantly different versus (a) normal control or (b) LPS or (c) LTG or (d) GBP ($p < 0.05$).

AchE and glutamate in animals administered combination in comparison to animals treated by single drug with significantly lower levels with LTG than GBP (Table 2, Figure 7).

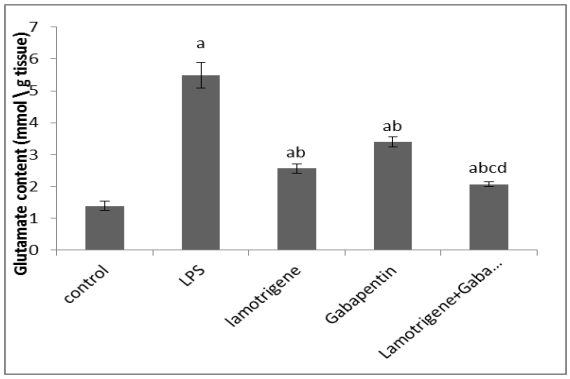

Figure 7. Effect of different treatments on glutamate content. Data shown are mean ± SD (n = 8 mice/group). Value significantly different versus (a) normal control or (b) LPS or (c) LTG or (d) GBP ($p < 0.05$). Effect of different treatments on histopathological changes of animal groups.

DISCUSSION

The intraperitoneal injection of LPS successfully induced neurobehavioral disturbances manifested by the significant differences between control and study animals regarding the neurobehavioral tests with significantly higher levels of brain tissue levels of MDA on one side and significantly lower levels of SOD and GSH on the other side, thus indicating a role for disturbed oxidant/antioxidant milieu for the pathogenesis of the reported neurobehavioral disturbance. Furthermore, the detected higher levels of acetylcholine esterase (AchE); a disturbance incriminated in the pathogenesis of AD, in the study versus control animals indicated that LPS-injection induced AD-like neurodegenerative state.

In support of the ability of induction of AD-like state by injection of LPS, Musa et al. (2017) reported that systemic exposure to LPS induces neuro-inflammation and memory deficit with increased MDA levels, reduced activities of antioxidants (SOD, GSH, GPx) with increased activity levels of AChE and pro-inflammatory cytokines. Andy et al. (2018) found LPS-induced neuroinflammation by induction of major pro-inflammatory mediators (iNOS and COX-2), pro-inflammatory cytokines and induced apoptotic neurodegeneration via stimulation of PARP-1, caspase-3 and cleaved caspase-3. Treatment with either LTG or GBP significantly ameliorated the effects of LPS injection on neurobehavioral tests, oxidative milieu and reduced AchE and glutamate contents with a significant difference, in favor of LTG. Moreover, using the combination of LTG & GBP significantly improved outcome both on neurobehavioral testing and on estimated markers

In line with the obtained results, Cooney et al. (2013) clinically tried GBP in low-dose for treating patients with vascular or mixed vascular/ Alzheimer Dementia with serious aggressive behavior and reported treatment tolerance that allowed control of aggressive conduct in those patients. Also, Suzuki & Gen (2015) in placebo-controlled study of AD patients with behavioral and psychological symptoms of dementia, found LTG therapy significantly decreased agitation scores with a significant decrease of diazepam dose, so suggested LTG therapy for patients with severe AD as it may be effectual and allow avoiding increased dosage of antipsychotic medications. Thereafter, Wang et al. (2016) suggest that LTG could improve brain inflammatory response and executive dysfunction in a mouse model of AD and recommended early LTG intervention as a promising therapeutic strategy for AD.

Multiple possible mechanisms were suggested for the reported effect of the studied drugs, where Kumar et al. (2012), using an animal model of 3-nitropropionic acid-induced neurotoxicity, found GBP and LTG treatments allowed the restoration of activities of antioxidant and mitochondrial complex enzymes with suppressing the production of pro-inflammatory cytokines and they attributed the reported significant improvement of behavioral changes to these effects. Also, Abelaira et al. (2013) detected increased SOD and catalase activities with reduction of protein kinase B in the amygdale of stressed rats on chronic LTG treatment and attributed the antidepressant-like effect of LTG in part to these effects. Kumar et al. (2014) using pentylenetetrazole-induced convulsions in mice, found Gab treatment reduced severity of convulsions, oxidative damage (demonstrated as elevated lipid peroxidation and nitrite concentration) and restored the activities of superoxide dismutase, reduced glutathione, catalase levels, and the depleted mitochondrial enzyme Complex (I, II, IV).

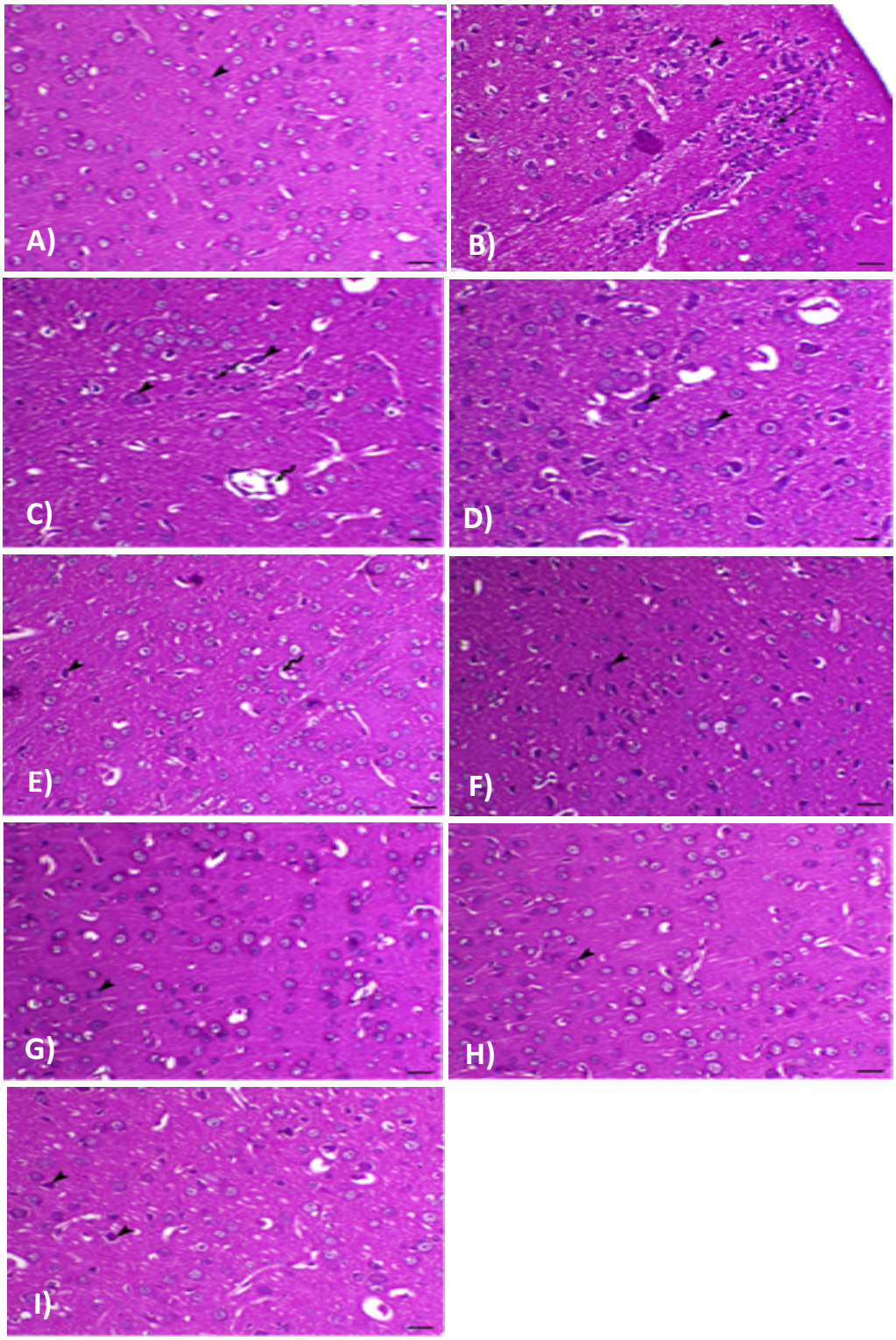

Figure 8. A) Brain of the normal animal showing normal neuronal cells (arrowhead) and fibers (background), B) Brain of LPS-treated animal showing ischemic neuronal injury (arrowhead) and focal gliosis (arrow), C) Brain of LPS-treated animal showing ischemic neuronal injury (arrowhead), focal gliosis (arrow) and perivascular oedema (curved arrow), D) Brain of LPS-treated animal showing marked ischemic neuronal injury (arrowheads), E) Brain of GBP-treated animal showing a mild degree of both ischemic neuronal injury (arrowhead) and perivascular edema (curved arrow), F) Brain of GBP-treated animal showing moderate degree of ischemic neuronal injury (arrowhead), G) Brain of LTG-treated animal showing a slight degree of ischemic neuronal injury (arrowhead), H) Brain of GBP+LTG treated animal showing slight degree of ischemic neuronal injury (arrowhead), I) Brain of GBP+LTG treated animal showing a mild degree of ischemic neuronal injury (arrowheads), H&E (200X, bar= 50 µm).

Thereafter, Wu et al. (2015), in a mouse model of AD, found chronic LTG therapy reduced amyloid-β plaques density with declined levels of β-C-terminal fragment of Aβ-protein precursor and enhanced activation of cAMP response element-binding protein, the two signaling pathways important for induction of autophagy. In another study, daily GBP treatment considerably attenuated oxidative stress with significant histological amelioration in the architecture of myelinated and unmyelinated fibers in a model of induced neuropathic pain in rats (Goel & Tyagi, 2016) It was found that administration of α2/δ subunit inhibitor, gabapentin, suppressed the signaling cascade of p38 mitogen-activated protein kinase by interrupting glutamate-signaling induced by voltage-gated Ca^{2+} channels inhibition, so GBP administration had neuroprotective effects following brain injury (Kim et al., 2017). Also, systemic GBP treatment was found to modulate N-methyl-D-aspartate receptors hyperactivity through inhibiting α2/δ-1, thus reduce calpain/caspase-3 activation in brain tissues (Luo et al., 2018). To our knowledge, this is the first study to investigate the role of LTG and GBP and their combination of LPS induced neurotoxicity.

CONCLUSION

Gabapentin and/or Lamotrigine therapy in LPS-induced AD, improved neurobehavioral testing, significantly restored oxidant/antioxidant milieu and significantly reduced acetylcholine esterase and glutamate contents in brain tissue. Combining both drugs showed favorable results compared to single-drug therapy. Thus, further clinical studies have to be conducted to validate their use in a clinical setting.

CONFLICT OF INTEREST

Authors declare that they have no conflicts of interest.

FUDING

There is no financial support for this study.

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Egyptian Association for Cancer Research (EACR)
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EACR is an NGO society that was declared by the Ministry of Social Solidarity (Egypt) No. 1938 in 19/11/2014 based on the initiative of Prof. Mohamed Labib Salem, the current Chairman of EACR. EACR aims primarily to assist researchers, in particular young researchers in the field of cancer research through workshops, seminars and conferences. Its first international annual conference entitled "Anti-Cancer Drug Discovery" was successfully organized in April 2019 (http://acdd.tanta.edu.eg). Additionally, EACR aims to raise the awareness of the society about the importance of scientific research in the field of cancer research in prediction, early diagnosis and treatment of cancer. EACR is also keen to outreach the scientific community with periodicals and news on cancer research including peer-reviewed scientific journals for the publication of cutting-edge research. The official scientific journal of EACR is "International Journal of Cancer and biomedical Research (IJCBR: https://jcbr.journals.ekb.eg) was successfully issued in 2017 and has been sponsored by the Egyptian Knowledge Bank (EKB: www.ekb.eg).

EACR Chairman,
Prof. Mohamed Labib Salem, PhD
Professor of Immunology
Faculty of Science, Tanta Universiy, Egypt

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