Life Sciences 217 (2019) 164–168

Contents lists available at ScienceDirect

Life Sciences

journal homepage: www.elsevier.com/locate/lifescie

Gastroprotective effect of memantine in indomethacin-induced peptic ulcer in rats, a possible role for potassium channels

Remon R. Rofaeil[a,b,*], Shereen S. Gaber[c]

[a] Department of Pharmacology, Faculty of Medicine, Minia University, Egypt
[b] Department of Pharmacology and toxicology, Faculty of Pharmacy, Deraya University, Egypt
[c] Department of Biochemistry, Faculty of Medicine, Minia University, Egypt

ARTICLE INFO

Keywords:
Memantine
Peptic ulcer
Potassium channels

ABSTRACT

Aims: Memantine is a commonly used drug in treating Alzheimer disease. In the current work, we aimed to evaluate the gastro-protective effect of memantine in indomethacin-induced peptic ulcer in rats.
Main methods: Peptic ulcer induced by indomethacin and memantine administered either alone or in combination with glibenclamide or nitric oxide synthase (NOS) inhibitor. Ulcer index done and malondialdehyde (MDA), superoxide dismutase (SOD), total nitrites, expression of tumor necrosis factor-α (TNF-α) and expression of nuclear factor kappa B (NF-κB) were measured in gastric mucosa.
Key findings: Memantine reduced ulcer index, reduced MDA, increased SOD, increased total nitrites and reduced expression of both TNF-α and NF-κB.

Glibenclamide and not NOS inhibitor abolished the gastroprotective effect of memantine.
Significance: Memantine was protective against indomethacin-induced peptic ulcer in rats mostly by affecting potassium channels, antioxidative stress and anti-inflammatory actions.

1. Introduction

The commonest cause of dementia is Alzheimer's disease (AD) which accounts for 50%–70% of all cases. AD, which occurs in old age, is accompanied by impaired cognition manifested by memory and judgment dysfunction together with increased morbidity, mortality, disability and dependence. Such disease results in a marked reduction in life quality [1].

On the other hand, arthritis is one of multimorbidity occurs with increasing age which also included cardiovascular disease (hypertension, cardiac disease), respiratory diseases, cerebrovascular diseases, diabetes and cancer [2].

One of the most commonly prescribed drugs in the world is Non-steroidal anti-inflammatory drugs (NSAIDs). It is used in either treatment or prophylaxis of rheumatoid arthritis, osteoarthritis, collagen disease, and ischemic cardiovascular or cerebrovascular disease due to their anti-inflammatory, analgesic, and anti-platelet effects. However, NSAIDs are well known to increase the risk of peptic ulcer with a 15% prevalence of gastric ulcer in endoscopic studies [3].

Furthermore, the complication of peptic ulceration is much more severe in old age with increased risk of in-hospital mortality [4].

Memantine, a noncompetitive *N*-methyl-D-aspartate (NMDA) receptor antagonist, was approved in the USA for the treatment of patients with moderate-to-severe dementia of AD with high efficacy [5].

In the current work, we aimed to evaluate the gastro-protective effect of memantine in acute gastric ulcer induced by indomethacin in rats. Furthermore, we aimed to find out the possible mechanism for such expected gastroprotective effect.

2. Material and methods

2.1. Animals

Male Wistar rats weighing 150–200 g were used throughout the present study. Rats were purchased from the National Research Center, Cairo, Egypt. Rats were housed in stainless steel cages offering individual housing. They were allowed free access to tap water and normal rats' diet (El-Nile Company, Egypt). All experimental protocols were approved by the animal care committee of Minia University and coincide with international guidelines.

2.2. Chemicals

Memantine was purchased from Copad Egypt for trade and

* Corresponding author at: Pharmacology Department, Faculty of Medicine, Minia University, Minia, Minia 61111, Egypt.
E-mail address: roshdyremon@yahoo.com (R.R. Rofaeil).

https://doi.org/10.1016/j.lfs.2018.12.005
Received 12 September 2018; Received in revised form 24 November 2018; Accepted 3 December 2018
Available online 06 December 2018
0024-3205/

pharmaceutical industries, Egypt, indomethacin was purchased from Nile co. for pharmaceuticals, glibenclamide was purchased from Sanofi-Aventis, Egypt and omega nitro-L-arginine (LNNA) was purchased from Sigma Aldrich, Germany. All other chemicals were of analytical grade and were obtained from commercial sources.

2.3. Experimental design

2.3.1. Experimental procedures

Rats were fed a standard diet of commercial rat chow and tap water and left to accommodate to the environment for at least one week before the start of the experiments. Rats were fasted for 24 h prior to the study. All experiments were performed at the same time of the day to avoid variations due to diurnal rhythms of putative regulators of gastric functions. Acute gastric ulceration was induced by indomethacin injection.

The animals were randomly divided into 5 experimental groups of 8–10 animals each. Group 1; control group, group 2; received indomethacin (40 mg/kg; i.p.) [6], group 3; received indomethacin and memantine (10 mg/kg; i.p.) [7], group 4; received indomethacin, memantine (10 mg/kg; i.p.) and glibenclamide (10 mg/kg; i.p.) [8] and group 5; received indomethacin, memantine (10 mg/kg; i.p.) and LNNA (25 mg/kg; i.p.) [9].

The stomach was washed with ice-cold saline and scored for macroscopic gross mucosal lesions and stored at −80 °C until used for assessment of gastric mucosal cells content of malondialdehyde (MDA), superoxide dismutase (SOD), total nitrites and expression of both tumor necrosis factor-α (TNF-α) and nuclear factor-kappa B (NF-κB).

2.3.2. Assessment of gastric mucosal lesions

Gastric mucosal lesions were expressed in terms of the ulcer index (U.I.). The severity factor is graded as follows; 0 for no lesions; 1 for petechae; 2 for erosions < 1 mm; 3 for erosions of 1–2 mm; 4 for erosions of 2–4 mm and 5 for erosions > 4 mm in length. The partial scores were then summated to obtain the ulcer index of the animal examined. The U.I. for each group was taken as the mean lesion score of all the rats in that group [10].

2.4. Preparation of tissue homogenates and measurements

Gastric mucosa was scraped and homogenized separately in potassium phosphate buffer 10 mM pH (7.4). The homogenates were centrifuged at 5000 rpm for 10 min at 4 °C. The resulting supernatant was used for determination of MDA level, total nitrites and SOD.

Malondialdehyde, a measure of lipid peroxidation, was evaluated by a method that depends on the reaction between MDA with thiobarbituric and the color developed was measured spectrophotometrically at 535 nm against a blank. Standard curve by 1,1,3,3-tetramethoxypropane was prepared. From this curve, the MDA concentration was expressed as nmol/g protein [11].

Gastric mucosal total nitrites, the stable oxidation end products of nitric oxide, served as an index of nitric oxide level and were measured by reduction of nitrate into nitrite using activated cadmium granules, followed by color development with Griess reagent in acidic medium [12].

Activity of SOD activity was measured by method of Marklund and Marklund [13] with a slight modification. This method is based on inhibition of the autoxidation of pyrogallol by SOD. The percentage of inhibition for the samples was calculated by the aid of running a control with no sample under the same conditions. SOD enzyme activity was expressed as U/mg protein, where one unit was defined as the amount of the enzyme that inhibited the rate of pyrogallol autoxidation by 50%.

2.5. Real time-PCR analysis

Gene expression of TNF-α and NF-κB in gastric mucosa cells were assessed using q RT-PCR technique. 100 mg frozen gastric mucosa was weighed and homogenized in 1 ml Trizol reagent (Invitrogen, USA). After incubating for 5–10 min at 25 °c, 0.2 ml chloroform was added to the homogenate and the mixture was shaken vigorously for 15 s, followed by 3 min incubation. Then the mixture was centrifuged at 4 °C, 10,000 g for 5 min. The upper layer of the mixture was obtained and 0.5 ml isopropanol was added into it. Next, the samples were centrifuged at 4 °C, 10,000*g* for 10 min. Supernatant was removed and the pellet was washed and suspended with 1 ml 75% ethanol.

Suspended pellet was centrifuged for 5 min at 4 °C, 7000 g. Majority of ethanol was removed and the remaining was air-dried. Completely dried pellet was dissolved and collected in 50 μl RNase free water. Quantity and quality of the extracted RNA were assessed by spectrometry. The concentrations and purity of RNA were determined by measuring the absorbance A260/A280. q RT-PCR for quantitative assessment of mRNA expression was performed on (Applied Biosyst 7500 fast, Techne (Cambridge) LTD., UK). RNA extract was reverse transcribed and q RT-PCR was performed according to manufacture instructions (Thermo Scientific one step kits plus ROX Vial, code no AB-4104/A).

The primer sequences were as following: GAPDH (internal control): Forward primer 5′-CCT GCC AAG TAT GAT GAC ATC AAG A-3′, Reverse primer 5′-GTA GCC CAG GAT GCC CTT TAG T-3′; NF-κB: Forward primer 5′-TGC TGT GCG GCT CTG CTT CC-3′, Reverse primer 5′-AGG CTG GGG TCT GCG TAG GG-3′ TNF-α: Forward primer 5′-CAG AGG GAA GAG TTC CCC AG -3′, Reverse primer 5′-CCT TGG TCT GGT AGG AGA CG-3′. All primers obtained from Eurofins Genomics, Europe. Real time polymerase chain reaction (RT- PCR) was performed with 0.2 μg RNA per reaction using 20 μL of SYBER Green qPCR mix containing 10 pM of specific primer in the REAL TIME PCR DETECTION SYSTEM. The SYBER Green data were analyzed with a relative quantification to GAPDH as reference gene.

The relative expression level of the gene calculated using formula $2^{-\Delta\Delta Ct}$ [14]. They were scaled relative to controls. The results for all experimental samples were graphed as relative expression compared with the control.

The reactions were as follows: reverse transcription step 42 °C for 15 min followed by an initial inactivation step at 95 °C for 10 min. The obtained cDNA was subjected to 35 cycles (15 s at 95 °C for denaturation followed by 60 s at 60 °C for annealing and extension). The level of expression of each target gene was normalized relative to the expression of GAPDH mRNA in that sample using $^{\Delta CT}$. relative differences in gene expression among groups were determined using comparative $^{\Delta\Delta CT}$ method and fold expression was calculated $2^{-\Delta\Delta CT}$, where $^{\Delta\Delta CT}$ represents $^{\Delta CT}$ values normalized relative to the mean $^{\Delta CT}$ of control sample.

2.6. Statistical analysis

Results were expressed as mean ± standard error (SE). Differences among groups were statistically analyzed by one-way analysis of variance (ANOVA), followed by Tukey's HSD post hoc test for multiple comparisons. For all tests, probability (p) was considered: Non-significant if P value ≥ 0.05, Significant if P value < 0.05. All data analyses were performed using Graph Pad Prism7 program.

3. Results

3.1. Effect of memantine and co-administered drugs on ulcer index

In both groups treated either with memantine alone or in combination with LNNA, there was a significant reduction in ulcer index, as compared to indomethacin treated group. Meanwhile, co-administration of glibenclamide with memantine showed ulcer index insignificant from indomethacin-treated group [Figs. 1A and 2].

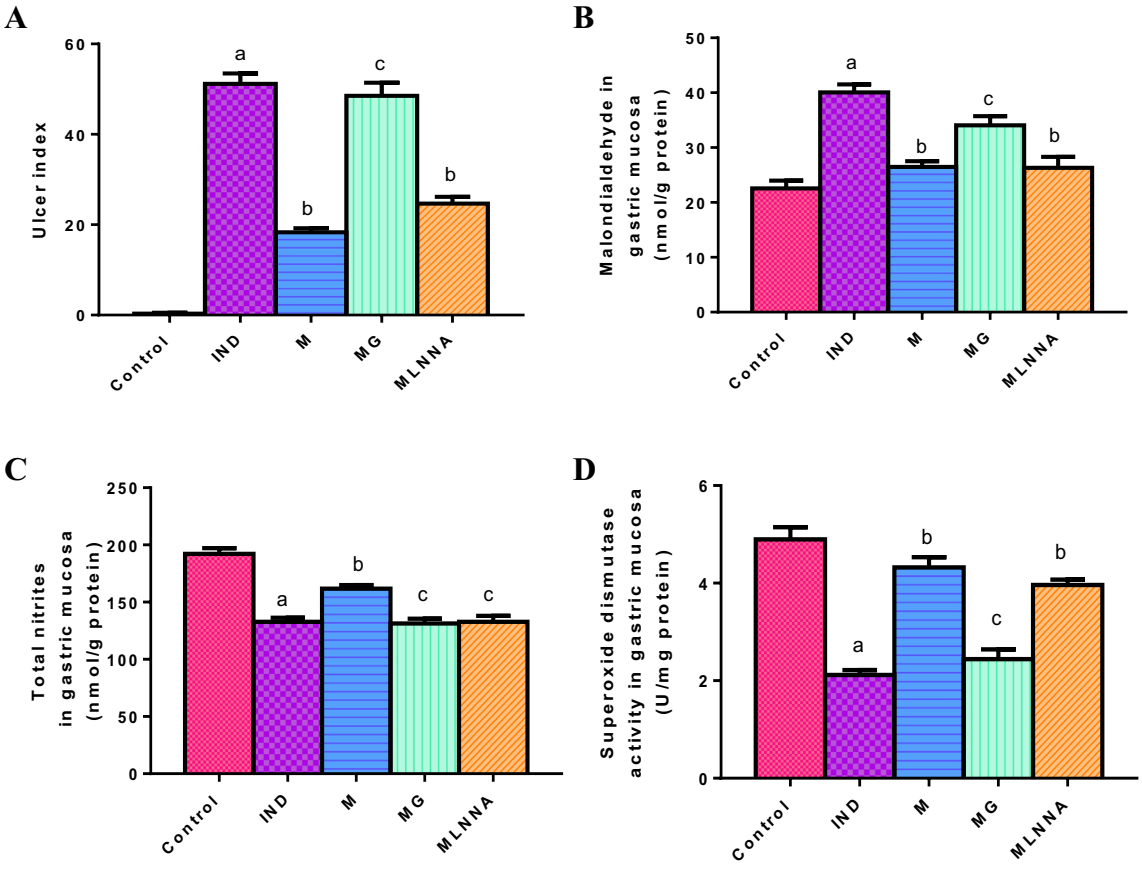

Fig. 1. Effect of memantine and co-administered drugs on ulcer index (A), malondialdehyde (B), total nitrites (C) and superoxide dismutase (D).
Results represent the mean ± SE (n = 8–10), [a]significant difference from control group, [b]significant difference from IND group, [c]significant difference from M group. [IND; indomethacin, M; memantine, G; glibenclamide and LNNA; omega nitro-L-arginine]. Significance is at $P < 0.05$.

3.2. Effect of memantine and co-administered drugs on malondialdehyde, total nitrites level and superoxide dismutase in gastric mucosa

Regarding MDA, in both groups treated with memantine alone or in combination with LNNA; there was a significant reduction, as compared to indomethacin treated group. In the same previous groups, there was a significant increase in SOD, as compared to indomethacin-treated group.

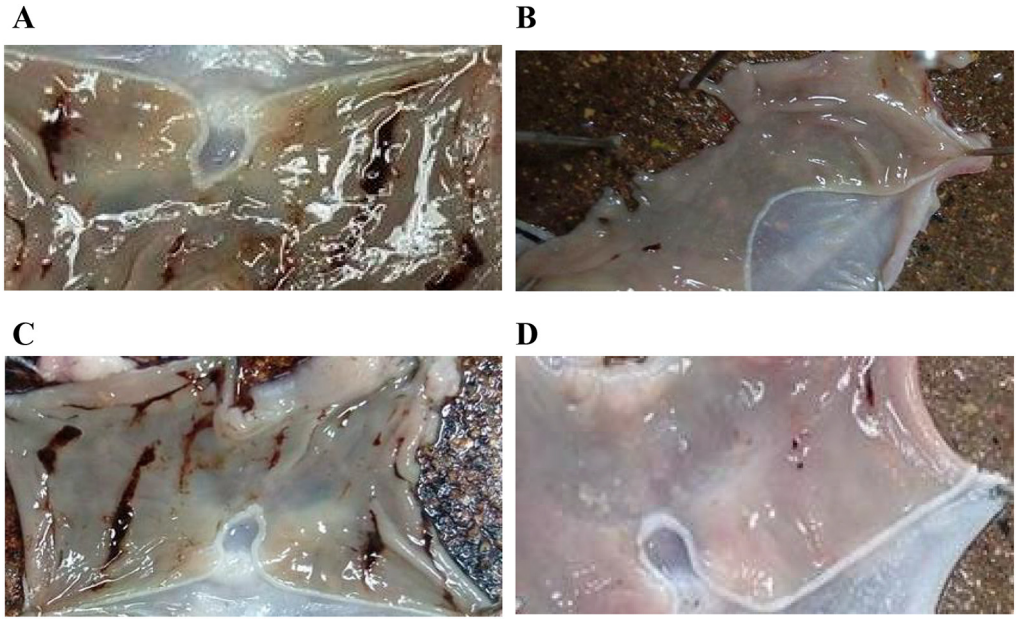

Fig. 2. The representative gross appearance of stomach with gastric mucosal lesions in IND group (A), M group (B), MG group (C) and MLNNA group (D). [IND; indomethacin, M; memantine, G; glibenclamide and LNNA; omega nitro-L-arginine].

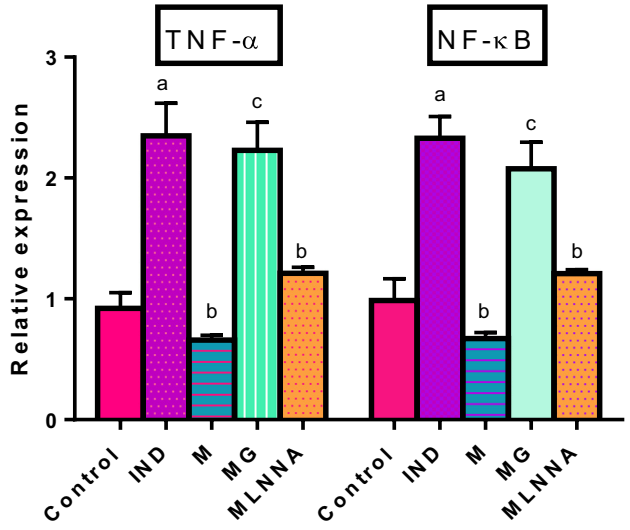

Fig. 3. Effect of memantine and co-administered drugs on gene expression of tumor necrosis factor-α and nuclear factor-Kappa B in gastric mucosa.
Results represent the mean ± SE (n = 8–10), [a]significant difference from control group, [b]significant difference from IND group, [c]significant difference from M group. [IND; indomethacin, M; memantine, G; glibenclamide and LNNA; omega nitro-L-arginine]. Significance is at $p < 0.05$.

At the same time, significant increase in total nitrites level in group treated with memantine, however, no change was noticed in group treated with memantine combined with LNNA, as compared to indomethacin treated group.

Surprisingly, co-administration of glibenclamide with memantine showed MDA level, SOD and total nitrites level insignificant from indomethacin-treated group and significant from memantine treated group [Fig. 1B, C and D].

3.3. Effect of memantine and co-administered drugs on gene expression of tumor necrosis factor-α and nuclear factor-kappa B

In both groups treated, either with memantine alone or in combination with LNNA, there was a significant reduction in gene expression of TNF-α and NF-κB, as compared to indomethacin treated group. Meanwhile, co-administration of glibenclamide with memantine showed gene expression of TNF-α and NF-κB insignificant from indomethacin-treated group [Fig. 3].

4. Discussion

Peptic ulcer may be induced by one of the most commonly prescribed drugs in the world; NSAIDs. Indomethacin traditional non-selective cyclooxygenase inhibitor with potent antipyretic, analgesic, and anti-inflammatory activity has been effectively used in the management of mild-to-moderate pain for > 50 years. It is commonly prescribed for the relief of acute gouty arthritis pain, but has demonstrated efficacy in the treatment of various other painful conditions, which increased with old age [15]. At the same time, memantine, one of the commonly used drugs in treatment Alzheimer disease, which usually occurs in old age [1].

The most common proposed mechanism for the ulcerogenic effect of indomethacin is the inhibition of the gastric cytoprotective mediators, prostaglandins, particularly due to the inhibition of COX pathway of arachidonic acid metabolism resulting in excessive production of leukotrienes and other products of 5-lipoxygenase pathway. The suppression of prostaglandins synthesis by NSAIDs results in increased susceptibility to mucosal injury and gastroduodenal ulceration, as well as, suppression of prostaglandins leads to reduction in the mucosal resistance and induction of oxidative stress and inflammatory status [16–18,and].

The results of this study indicate that memantine displays an anti-ulcer effect; it significantly reduced indomethacin-induced gastric ulcer index. Memantine antagonized oxidative stress induced by indomethacin, which evidenced by significant reduction in MDA level together with significant increase in SOD and total nitrites in gastric mucosa. This finding is in agreement with previous studies, which reported the anti-oxidative stress action of memantine in different models of cell injury [19,20].

Regarding anti-inflammatory effect, memantine antagonized inflammation induced by indomethacin evidenced by reduction in TNF-α and NF-κB expression. Similarly, It was reported that memantine exerts anti-inflammatory action in neurodegenerative conditions by reducing many inflammatory mediators including many cytokines [21,22]. It was also reported the anti-inflammatory action of memantine in colon ulcerations evidenced by reduction in TNF-α and interleukins [23]. At the same time, previous study reported that memantine has protective effect against cell damage and neurodegeneration through anti-inflammatory actions [24].

Surprisingly, co-administration of glibenclamide, potassium channel blocker, with memantine abolished the gastroprotective effect of memantine, which shown by significant increase in ulcer index. This effect explained by ameliorating the anti-oxidative stress and anti-inflammatory actions of memantine shown by increase in MDA together with reduction in SOD and increase in both TNF-α and NF-κB expression in gastric mucosa. This finding opens a gate for explaining the gastroprotective effect of memantine by activating potassium channels.

There is a correlation between K^+ channels and gastric acid secretion by “No Potassium, No Acid” [25]. This finding is supported with the finding that GI ulceration is intermittently reported in these patients with the use of K^+ supplements [26]. Furthermore, it was reported that K^+ channels are regulated by NSAIDs and the mechanism of GI ulceration by NSAIDs may be through a direct cytotoxic effect on mucosal cell causing injury and damage and that NSAIDs stimulate K^+ efflux and increase the permeability of cell membrane [27,28].

Another finding support the role of Some of these NSAIDs have been also identified as openers of ATP-sensitive K^+ (K^+_{ATP}) channels, members of the K_{ir} family, which participate in the antinociception in both the central and the peripheral nervous system [29]. Running in the same stream, celecoxib, a selective inhibitor of COX-2, which is well known to have no effect on mucoprotective PG synthesis, inhibits many voltage-gated ion channels including KCNQ1 (K_v7.1) that are regulatory channels of gastric acid secretion. So that, it might be the changes in the potassium channel in GI epithelial cells increase membrane permeability, which induces mucosal barrier defects and initiates ulceration [30].

The previous mechanism supported by the gastroprotective effect of nicorandil and diazoxide, which possess K^+_{ATP} channel activating property and showed anti-oxidative stress and anti-inflammatory actions [31–33,and]. All this information elaborates that altered potassium channel and development of ulceration in GI tract are closely related.

At the same time, LNNA, NOS inhibitor, co-administration with memantine did not abolished the gastroprotective effect of memantine evidenced by the significant reduction in ulcer index. Neither anti-oxidant action nor anti-inflammatory action of memantine was affected with LNNA co-administration, which was shown by the persistence of reduction in MDA, increase in SOD levels, reduction of TNF-α and NF-κB in gastric mucosa occurred with memantine monotherapy. These findings exclude the role of nitric oxide in the gastroprotective effect of memantine in the current study.

Although previous studies reported that NO activates guanylyl cyclase to increase cyclic guanosine monophosphate (cGMP) levels and subsequently activates the ATP sensitive potassium channels (K + ATP) and that the activation of this NO/cGMP/K + ATP pathway leads to gastroprotection [34], in the current work such link was not shown.

However, in agreement with the current study, it was reported that the gastroprotective of alpha-bisabolol was not affected when pretreated with NOS inhibitor and at the same time, the alpha-bisabolol effect was significantly reduced in rats pretreated with glibenclamide [35]. Similarly, menthol was reported to exert gastroprotective effect, which was mediated by potassium channel activation without increasing nitric oxide, which excludes the role of nitric oxide in activating potassium channel in such gastroprotective effect of menthol [36]. Furthermore, the current results are supported by the finding that in some conditions the increase in potassium channels activity may be unlinked to nitric oxide and that potassium channels are not exclusively activated by nitric oxide as it may affected by prostaglandins [37].

In conclusion, memantine has a gastroprotective effect through antagonizing oxidative stress and inflammation induced by indomethacin in rats. Co-administration of potassium channel blocker abolished this gastroprotective effects, so that, a possible role for potassium channel is suggested.

References

[1] A. Villarejo Galende, M. Eimil Ortiz, S. Llamas Velasco, M. Llanero Luque, C. Lopez de Silanes de Miguel, C. Prieto Jurczynska, Report by the Spanish Foundation of the Brain on the social impact of Alzheimer disease and other types of dementia, Neurologia (Barc. Spain) (2017), https://doi.org/10.1016/j.nrl.2017.10.005 pii: S0213-4853(17)30350-X.

[2] A. Granic, N. Mendonca, A.A. Sayer, T.R. Hill, K. Davies, A. Adamson, et al., Low protein intake, muscle strength and physical performance in the very old: the Newcastle 85+ Study, Clin. Nutr. (Edinb. Scotl.) 37 (6 Pt A) (2017) 2260–2270.

[3] S.J. Shin, C.K. Noh, S.G. Lim, K.M. Lee, K.J. Lee, Non-steroidal anti-inflammatory drug-induced enteropathy, Intest. Res. 15 (2017) 446–455.

[4] M. Cheng, W.H. Li, M.T. Cheung, Early outcome after emergency gastrectomy for complicated peptic ulcer disease, Hong Kong Med. J. 18 (2012) 291–298.

[5] M.M. Koola, R.W. Buchanan, A. Pillai, K.J. Aitchison, D.R. Weinberger, S.T. Aaronson, et al., Potential role of the combination of galantamine and memantine to improve cognition in schizophrenia, Schizophr. Res. 157 (2014) 84–89.

[6] S.L. Elliott, R.J. Ferris, A.S. Giraud, G.A. Cook, M.V. Skeljo, N.D. Yeomans, Indomethacin damage to rat gastric mucosa is markedly dependent on luminal pH, Clin. Exp. Pharmacol. Physiol. 23 (1996) 432–434.

[7] E. WoldeMussie, E. Yoles, M. Schwartz, G. Ruiz, L.A. Wheeler, Neuroprotective effect of memantine in different retinal injury models in rats, J. Glaucoma 11 (2002) 474–480.

[8] A.R. Ribeiro, P.B. Diniz, M.S. Pinheiro, R.L. Albuquerque-Junior, S.M. Thomazzi, Gastroprotective effects of thymol on acute and chronic ulcers in rats: the role of prostaglandins, ATP-sensitive K(+) channels, and gastric mucus secretion, Chem. Biol. Interact. 244 (2016) 121–128.

[9] B. Veeresh, B.M. Patil, S.V. Veeresh Babu, N.M. Jeedi, B.S. Unger, Involvement of nitric oxide in 5-HT(3) receptor agonist-induced fluid accumulation in jejunum and colon of anesthetized rats, Indian J. Pharm. 41 (2009) 221–223.

[10] M. Till, T. Gati, K. Rabai, D. Szombath, J.I. Szekely, Effect of [D-Met2,Pro5]enkephalinamide on gastric ulceration and transmucosal potential difference, Eur. J. Pharmacol. 150 (1988) 325–330.

[11] J.A. Buege, S.D. Aust, Microsomal lipid peroxidation, Methods Enzymol. 52 (1978) 302–310.

[12] K.V. Sastry, R.P. Moudgal, J. Mohan, J.S. Tyagi, G.S. Rao, Spectrophotometric determination of serum nitrite and nitrate by copper-cadmium alloy, Anal. Biochem. 306 (2002) 79–82.

[13] S. Marklund, G. Marklund, Involvement of the superoxide anion radical in the autoxidation of pyrogallol and a convenient assay for superoxide dismutase, Eur. J. Biochem. 47 (1974) 469–474.

[14] H.D. VanGuilder, K.E. Vrana, W.M. Freeman, Twenty-five years of quantitative PCR for gene expression analysis, BioTechniques 44 (2008) 619–626.

[15] S. Nalamachu, R. Wortmann, Role of indomethacin in acute pain and inflammation management: a review of the literature, Postgrad. Med. 126 (2014) 92–97.

[16] M.A. Morsy, M.A. El-Moselhy, Mechanisms of the protective effects of curcumin against indomethacin-induced gastric ulcer in rats, Pharmacology 91 (2013) 267–274.

[17] N.E. El-Ashmawy, E.G. Khedr, H.A. El-Bahrawy, H.M. Selim, Gastroprotective effect of garlic in indomethacin induced gastric ulcer in rats, Nutrition (Burbank Los Angel. County, Calif.) 32 (2016) 849–854.

[18] J.M. Lehmann, J.M. Lenhard, B.B. Oliver, G.M. Ringold, S.A. Kliewer, Peroxisome proliferator-activated receptors alpha and gamma are activated by indomethacin and other non-steroidal anti-inflammatory drugs, J. Biol. Chem. 272 (1997) 3406–3410.

[19] A.A. Abdel-Hamid, D. Firgany Ael, E.M. Ali, Effect of memantine: a NMDA receptor blocker, on ethambutol-induced retinal injury, Ann. Anat. Anat. Anz. 204 (2016) 86–92.

[20] S.N. Amin, A.A. El-Aidi, M.B. Zickri, L.A. Rashed, S.S. Hassan, Hepatoprotective effect of blocking *N*-methyl-d-aspartate receptors in male albino rats exposed to acute and repeated restraint stress, Can. J. Physiol. Pharmacol. 95 (2017) 721–731.

[21] S.L. Chen, P.L. Tao, C.H. Chu, S.H. Chen, H.E. Wu, L.F. Tseng, et al., Low-dose memantine attenuated morphine addictive behavior through its anti-inflammation and neurotrophic effects in rats, J. Neuroimmune Pharmacol. 7 (2012) 444–453.

[22] M. Gubandru, D. Margina, C. Tsitsimpikou, N. Goutzourelas, K. Tsarouhas, M. Ilie, et al., Alzheimer's disease treated patients showed different patterns for oxidative stress and inflammation markers, Food Chem. Toxicol. 61 (2013) 209–214.

[23] E. Motaghi, V. Hajhashemi, P. Mahzouni, M. Minaiyan, The effect of memantine on trinitrobenzene sulfonic acid-induced ulcerative colitis in mice, Eur. J. Pharmacol. 793 (2016) 28–34.

[24] X. Wei, H. Gao, J. Zou, X. Liu, D. Chen, J. Liao, et al., Contra-directional coupling of Nur77 and Nurr1 in neurodegeneration: a novel mechanism for memantine-induced anti-inflammation and anti-mitochondrial impairment, Mol. Neurobiol. 53 (2016) 5876–5892.

[25] D. Heitzmann, R. Warth, No potassium, no acid: K+ channels and gastric acid secretion, Physiology (Bethesda) 22 (2007) 335–341.

[26] C.E. Leijonmarck, L. Raf, Ulceration of the small intestine due to slow-release potassium chloride tablets, Acta Chir. Scand. 151 (1985) 273–278.

[27] L.M. Lichtenberger, Where is the evidence that cyclooxygenase inhibition is the primary cause of nonsteroidal anti-inflammatory drug (NSAID)-induced gastrointestinal injury? Topical injury revisited, Biochemical pharmacology. 61 (2001) 631–637.

[28] W. Tomisato, K. Tanaka, T. Katsu, H. Kakuta, K. Sasaki, S. Tsutsumi, et al., Membrane permeabilization by non-steroidal anti-inflammatory drugs, Biochem. Biophys. Res. Commun. 323 (2004) 1032–1039.

[29] M. Ocana, C.M. Cendan, E.J. Cobos, J.M. Entrena, J.M. Baeyens, Potassium channels and pain: present realities and future opportunities, Eur. J. Pharmacol. 500 (2004) 203–219.

[30] R.V. Frolov, S. Singh, Celecoxib and ion channels: a story of unexpected discoveries, Eur. J. Pharmacol. 730 (2014) 61–71.

[31] H.A. Ismail, M.M. Khalifa, M.K. Hassan, O.M. Ashour, Insights in the mechanisms underlying the anti-ulcer activity of nicorandil, Pharmazie 62 (2007) 60–66.

[32] H.M. Patel, D.D. Santani, S.G. Goswami, Evaluation of the effects of nicorandil on experimentally induced gastric ulcers, Pharmacology 63 (2001) 154–159.

[33] M. Rahgozar, H. Pazokitoroudi, A. Bakhtiarian, B. Djahanguiri, Diazoxide, a K(ATP) opener, accelerates restitution of ethanol or indomethacin-induced gastric ulceration in rats independent of polyamines, J. Gastroenterol. Hepatol. 16 (2001) 290–296.

[34] J.V. Medeiros, G.G. Gadelha, S.J. Lima, J.A. Garcia, P.M. Soares, A.A. Santos, G.A. Brito, R.A. Ribeiro, M.H. Souza, Role of the NO/cGMP/K(ATP) pathway in the protective effects of sildenafil against ethanol-induced gastric damage in rats, Br. J. Pharmacol. 153 (2008) 721–727.

[35] S.B. Bezerra, L.K. Leal, N.A. Nogueira, A.R. Campos, Bisabolol-induced gastroprotection against acute gastric lesions: role of prostaglandins, nitric oxide, and KATP+ channels, J. Med. Food 12 (2009) 1403–1406.

[36] A.L. Rozza, C.A. Hiruma-Lima, R.K. Takahira, C.R. Padovani, C.H. Pellizzon, Effect of menthol in experimentally induced ulcers: pathways of gastroprotection, Chem. Biol. Interact. 206 (2013) 272–278.

[37] S.R. Lira, V.S. Rao, A.C. Carvalho, M.M. Guedes, T.C. de Morais, A.L. de Souza, et al., Gastroprotective effect of lupeol on ethanol-induced gastric damage and the underlying mechanism, Inflammopharmacology 17 (2009) 221–228.