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Effect synergistic of gabapentin with hydrogen peroxide on neurotransmitters and antioxidants in chicken chicks.

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ABSTRACT

The place where the experiment was conducted was the animal house. The duration was 30 days, the number of birds was 60, and their weights ranged from 75 grams - 110 grams. Also, the dose of gabapentin used was 990 mg/kg.

The aim of this study was to know the effect of oxidative stress induced by hydrogen peroxide on the drug response to gabapentin and to compare this effect with normal chicks, as well as to know the effect of oxidative stress on neurotransmitters (kappa and glutamate), and antioxidants (malonaldehyde and glutathione).

Giving hydrogen peroxide caused oxidative stress in chicken chicks in a significant way through a significant increase in the concentration of malondialdehyde and a significant decrease in the concentration of glutathione. In addition, giving gabapentin increased this effect in stressed chicken chicks compared to normal chickens.

Giving gabapentin resulted in a significant increase in the neurotransmitter kappa while keeping the concentration of glutamate close to the negative control group, while hydrogen peroxide caused an increase in the concentration of both the neurotransmitters kappa and glutamate. In addition, giving gabapentin and hydrogen peroxide worked together to significantly increase both kappa and glutamate.

We conclude from this study that oxidative stress induced by hydrogen peroxide in chicken chicks led to an increase in the pharmacological effectiveness of gabapentin, in addition to the occurrence of harmful toxic effects at the level of neurotransmitters and antioxidants.

Introduction

Gabapentin is a drug derived from a group of compounds known as (Amino methyl)5-methylhexanoic acid) -s-3), and is similar in structure to the neurotransmitter Gamma-Aminobutyric Acid (GABA). Gabapentin is classified as a first-generation anticonvulsant drug, in when followed by pregabalin of the second generation. Gabapentin interacts with α2δ1 class receptors associated with P/Q type, voltage-dependent calcium channels [1].

It affects the nervous system by affecting voltage-gated calcium channels bound to α2δ1 receptors in the presynaptic area. This effect modulates the transmission of nerve signals, can contribute to effects such as pain relief, and reduced seizures. This is according to recent research [2] Gabapentin is used to: treat nerve pain and neuropathy in humans and animals [3] and reduce anxiety and generalized anxiety disorders [4] .

Oxidative stress is an increase in free radicals within the cells of living organisms because of exposure to oxidizing compounds such as hydrogen peroxide. This type of stress indicates a malfunction in the internal mechanisms that protect cells from the harmful effects of oxidative stress. Concentrations of compounds such as glutathione and malondialdehyde are measured in the body to be used as indicators of the level of oxidative stress. Oxidative stress can lead to negative effects on the nervous system and drug response, and the effectiveness of some anesthetic and sedative medications may be affected due to this effect [5].

Materials and methods

Within the framework of this study, we relied on broiler chickens of the Ross family, of both male and female, as a study subject. A total number of 60newly hatched chicks were collected from the Qandil hatchery located in Erbil Governorate. Upon the arrival of these chicks, they were transferred to specially design breeding cages, which come in dimensions (200 x 200 x 150 cm), according to specific and standard conditions.

These chicks were provided with a clean environment, unpolluted water, and balanced nutrition. They were raised for an appropriate period before conducting the experiments and a period between 7 -15 days of age was chosen. Careful attention was taken to ensure optimal conditions for these chicks during this period, to ensure that the experiments, were conducted with high efficiency and accuracy.

Study design of the current experiment:

A total number 60 then divided into four groups, and each group included 15 chicks

• The first group, negative control: was given physiological saline solution orally for 30 days.

• The second group (gabapentin): was dosed with gabapentin (990 mg/kg) orally for 30 days.

The above two groups were provided with normal drinking water throughout the study period.

• The third group (hydrogen peroxide group): was given physiological saline solution orally for 30 days and was considered a positive control.

• The fourth group (gabapentin with hydrogen peroxide group): was dosed with gabapentin (990 mg/kg) orally for 30 days

The above two groups were provided with hydrogen peroxide (0.5% with drinking water) throughout the study period.

Collect blood samples

After 30 days had passed since the last dose in the experiment for all groups and after the end of the dosing period, The blood was drawn directly from the heart (heart puncture), and blood was also taken by cutting the jugular vein to obtain an amount of (5 ml) of blood and it was transferred in a tube (Gel tube) does not contain an anticoagulant.

Then, the separation process was carried out using a centrifuge at a speed of (3000) rpm for (15) minutes. After completing this process, the serum was transferred to test tubes specially designed for this purpose, and stored at a temperature of (-20) degrees Celsius. All these steps were carried out with care and attention to ensure that the quality of the samples and the various chemical components in the blood serum were kept in deep freeze.

Biochemical markers

Estimation of glutamate enzyme concentration and Concentration estimate Chicken Gamma-Aminobutyric Acid (GABA)

The concentration of glutamate was determined using a specific analysis kit produced by the Chinese company Sunlong. The procedures mentioned in the instructions included with the kit were followed to estimate the glutamate concentration.

The concentration of gamma-aminobutyric acid in chickens was determined using a specific analysis kit produced by the Chinese company Sunlong. The procedures mentioned in the instructions included with the kit were followed.

Evaluation of malondialdehyde concentration

The researchers [6] used a modified thiobarbituric acid (TBA) reaction method to measure levels of MAD (Malondialdehyde), which is an end product of the lipid peroxidation process and represents an indicator of this process. The measurement is based on the reaction between pyrene and lipid peroxides, especially malondialdehyde, with thiobabituric acid in a pH-dependent medium**.**

Glutathione concentration in blood serum

Serum glutathione level was estimated using the Ellman reagent method [7].

Statistical analysis s by one way –ANOVA, Post –Hoc Duncan′s test.

Results and Discussion

Assessment of Effect of Gabapentin with Hydrogen Peroxide on Neurotransmitters

Assessment of Effect of Gabapentin with Hydrogen Peroxide on Glutamate

This table presents the mean values and standard deviation of the level of neurotransmitters (glutamate) in the different groups that were studied. The columns in the table represent the different groups, while the rows contain the average Glutamate levels for each group.

Table 1: The effect of gabapentin and hydrogen peroxide on the level of the neurotransmitters (glutamate) and (GABA)

the test (Mean +S. E) / ***Groups***	GABA	Glutamate
control group	350.50 ± 33.5	18.90±2.2
Hydrogen peroxide group	398.20 ±42.1	22.05±1.6
Gabapentin group	367.75. ± 39.8	19.80±2.0
Gabapentin combination with hydrogen peroxide	444.30 ± 47.9	24.30±3.2
Probability level P- Value	0.001**	0.001**

✓ Analysis by one way –ANOVA, Post –Hoc Duncan′s test.

 Same letter significant difference while different letter non – significant

 Significant differences at p<0.05, ** highly significant level <0.01

Control group represents normal, where the average level of neurotransmitters (glutamate) is estimated when there are no interventions.

Hydrogen peroxide group represents the treatment with hydrogen peroxide, and shows a significant increase in the level of neurotransmitters (glutamate) compared to the control group, which indicates its effect on the level of this neurotransmitter. The gabapentin group showed a slight but non-significant increase in the level of neurotransmitters (glutamate) compared to the control group. Gabapentin combination with hydrogen peroxide showed a significant and significant increase in the level of neurotransmitters (glutamate) compared to the control group and the rest of the groups. This high effect indicates a possible interaction between gabapentin and hydrogen peroxide in increasing the level of neurotransmitters glutamate [8]. As for the effect of gabapentin and hydrogen peroxide on the level of GABA. The hydrogen peroxide group showed a significant increase in the level of GABA compared to the control group, which indicates the effect of hydrogen peroxide on increasing the concentration of GABA in the brain.

On the other hand, the gabapentin group also showed a significant increase in the level of GABA compared to the control group, and this may indicate the effect of gabapentin on enhancing the secretion of GABA in the brain.

As for the gabapentin group with hydrogen peroxide, there was a significant increase in the level of GABA compared to the control group, as well as the gabapentin group alone. This combined effect may indicate a reinforcing interaction between gabapentin and hydrogen peroxide in promoting GABA secretion and elevation in the brain. This potential effect could have important effects on central nervous system functions and neuronal homeostasis in the body.

This increase in the level of neurotransmitters may be an indication of the negative effect of hydrogen peroxide on the functions of neurons and may have harmful effects on the nervous system and its functions [9].

The effect that hydrogen peroxide can have on neurotransmitters, such as glutamate, can occur in many ways, including affecting the central nervous system and interacting with chemical signaling processes within neurons. The most prominent potential effects are:

Oxidative stress and free radical formation Hydrogen peroxide increases oxidative stress within cells, leading to the formation of free radicals. These free radicals may lead to cell damage and unwanted chemical reactions that affect the function of neurotransmitters [10].

Effect on the function of ion channels Hydrogen peroxide may affect the function of ion channels in the cell membrane of neurons. This effect can lead to a change in the flow of ions into and out of cells, affecting the balance of electrical charges and nerve signals [11].

Interaction with cellular proteins Hydrogen peroxide may interact with proteins within nerve cells, which can modify their function and thus

influence nerve signaling and neurotransmitter function. [12].

The effect of gabapentin on glutamate neurotransmitters in the brain represents a complex and specialized field of study that requires in-depth and careful investigation. A number of potential biochemical and molecular processes may interact to produce the effect of gabapentin on neurotransmitters:

Effect on Electrical Channels Gabapentin may modulate the activity of electrical channels in nerve cells, affecting the reception of nerve signals and the release of neurotransmitters [13].

Effect on calcium extraction Gabapentin may affect the process of calcium extraction from nerve cells, leading to changes in calcium balance and thus affecting the process of neurotransmitter secretion [14]

Effect on gabapentin activity thought to be related to kappa (gamma-aminobutyric acid), an important neurotransmitter that affects the regulation of nerve signals, impulse control, and pain [15]

The effect of gabapentin on the level of GABA is due to its interference with N-type calcium channels and P/Q-type calcium channels in nerve cells. These calcium channels play an essential role in signal transduction and GABA secretion. When calcium channels are activated, calcium is brought into neurons, stimulating the secretion of GABA. Gabapentin indirectly inhibits the activity of these calcium channels by affecting N-type and p/Q-type calcium channels in neurons. This effect leads to reduced calcium influx into neurons, which reduces GABA secretion [16].

So, we can explain the increase in the concentration of GABA in the brain when taking gabapentin because the drug inhibits the flow of calcium to nerve cells and thus reduces the secretion of GABA. This effect can contribute to calming the nervous system and reducing nerve stimulation, which contributes to the improvement of epilepsy and the relief of nerve pain.

This interpretation sheds light on the complex effect of gabapentin on calcium channels and thus on GABA secretion and its role in regulating neuronal activity in the brain [17].

This interaction effect between gabapentin and hydrogen peroxide could have a combined effect on the function of calcium channels and thus the influx of calcium (Ca2+) into the cell. This combined effect can lead to abnormal regulation of cellular calcium (Ca2+) levels, potentially affecting complex cellular processes and biochemical pathways involved in cell function and signal transduction.

Measuring the effect of gabapentin with hydrogen peroxide on antioxidants (malondialdehyde and glutathione).

Table (2) shows an estimate of the effect of gabapentin with hydrogen peroxide on malondialdehyde (MDA) levels. The table presents average values with standard errors (Mean + S.E.) for malondialdehyde (MDA) levels under different test conditions.

Table 2: Effect of gabapentin and hydrogen peroxide on oxidative stress marker.

Mean +S. / Groups	MDA	GSH
control group	3.07± 0.06	9.89±0.36
Hydrogen peroxide group	4.12 ±0.52	8.65±0.36
Gabapentin group	2.984± 0.11	9.136±0.36
Gabapentin combination with hydrogen peroxide	4.535±0.388	7.767±0.15
Probability level P- Value	0.001**	0.001**

✓ Analysis by one way –ANOVA, Post –Hoc Duncan′s test.

 Same letter significant difference while different letter non – significant

 Significant differences at p<0.05, ** highly significant level <0.01

The table shows the MDA levels measured for each experimental group. The control group represents the baseline MDA level, while the hydrogen peroxide group and the gabapentin group show the effects of hydrogen peroxide and gabapentin on MDA levels, respectively. The last group, the gabapentin plus hydrogen peroxide combination, shows the combined effect of gabapentin and hydrogen peroxide on MDA levels.

The probability level shows a P-value for statistical analysis of 0.001**, which indicates a highly significant difference. This table indicates that the combination of gabapentin with

hydrogen peroxide leads to a significant increase in MDA levels compared to the single treatments or the control group, as indicated by the statistical significance of the difference. These results indicate a possible interaction between gabapentin and hydrogen peroxide that could influence oxidative stress and lipid peroxidation, as expressed in MDA levels.

The results suggest an estimate of the effect of gabapentin combined with hydrogen peroxide on antioxidant levels. In the section, the effect of this compatibility on the level of malondialdehyde (MDA), an indicator of oxidative stress and lipid peroxidation, was estimated.

Table 2 showed the mean values with standard errors for MDA levels in different groups. The control group represented a basal level of MDA, while the hydrogen peroxide group showed

This is because hydrogen peroxide (H2O2) is a compound consisting of two oxygen atoms, and is derived from water. When considering how hydrogen peroxide raises the level of Malone dialdehyde (MDA), which is an indicator of lipid peroxidation and oxidative stress, we can relate this to its effect on the oxidation-reduction system in cells. Hydrogen peroxide is a strong oxidant, and when it reacts with molecules and compounds within cells, it may cause oxidation reactions that lead to the formation of free radicals. These free radicals can do damage to vital parts inside cells, including cell membranes and basic components of cells [18]. There are some possible effects of hydrogen peroxide on raising the level of MDA and increasing oxidative stress in cells:

Oxidation Reactions Hydrogen peroxide can lead to direct oxidation reactions with lipids in the cell membrane and cell components. These reactions produce compounds called oxidation indicator compounds, including Malone dialdehyde (MDA). Iron Reactions Hydrogen peroxide may enhance iron reactions that cause the formation of free iron radicals, which are oxidation-indicating compounds that may cause damage within cells. Increased presence of hydrogen peroxide can increase the level of oxidative stress in cells. This can lead to cascade redox reactions and activation of oxidative stress pathways within the cell [19].

As for the reasons for these findings, the increase in MDA levels could be due to a combined interaction between gabapentin and hydrogen peroxide that leads to an increase in oxidative stress. Hydrogen peroxide is a molecule that leads to oxidative stress when its concentration is increased, and the interaction between it and gabapentin may lead to interactions that lead to an increase in the formation of MDA.

These results could be of interest in explaining the effects of gabapentin and hydrogen peroxide on the redox homeostasis in the body, and suggest that there are chemical interactions that may play a role in increasing oxidative stress and the formation of MDA.

The possible mechanism suggests that the reaction of hydrogen peroxide with gabapentin extract may lead to the formation of increased oxidation reactions inside the cell. These reactions promote oxidative stress and the generation of oxidative stress-indicating molecules such as Malon dialdehyde (MDA). Thus, the elevation in MDA could be due to a combined reaction between hydrogen peroxide and gabapentin that leads to an increase in oxidative stress and the formation of oxidative stressors in cells [20].

Table (2) provides an analysis of the effect of combining gabapentin with hydrogen peroxide on glutathione (GSH) levels. Glutathione is a vital antioxidant that plays an important role in maintaining cell health and protecting them from oxidative stress. The experiment was conducted with four different groups, each group was exposed to a specific treatment. The mean values (expressed as mean ± standard error) of glutathione levels for each group are presented as follows:

Control group: The control group, which did not receive any treatment, showed an average glutathione level of 9.89 ± 0.36. Hydrogen peroxide group: The hydrogen peroxide-treated group showed a lower mean glutathione level of 8.65 ± 0.36 compared to the control group. This suggests that exposure to hydrogen peroxide may have reduced glutathione levels. Gabapentin group: The gabapentin-treated group showed a mean glutathione level of 9.136 ± 0.36. Interestingly, the glutathione level in this group remained fairly similar to that in the control group. Gabapentin combination with hydrogen peroxide:

The group exposed to both gabapentin and hydrogen peroxide showed a significantly lower mean glutathione level of 7.767 ± 0.15. This decrease in glutathione levels in the presence of both compounds indicates a potential interaction that may negatively affect glutathione levels. The P value associated with these observations is

0.001**, which indicates statistical significance, as it is lower than the usual significance level of 0.05 used. This indicates that there is a statistically significant difference between the groups in terms of glutathione levels.

The decrease in glutathione levels in the hydrogen peroxide group may be due to oxidation reactions that occur as a result of cells being exposed to this powerful compound. Hydrogen peroxide contains two oxygen atoms, and it can increase the presence of active oxygen within cells. When hydrogen peroxide reacts with compounds within the cell, oxidation reactions can occur that lead to the production of oxidation indicator molecules. Glutathione is an important natural antioxidant found in cells, and it works to protect cells from damage resulting from oxidative reactions. When the body is exposed to strong oxidizing compounds such as hydrogen peroxide, glutathione levels can become depleted as a result of trying to combat these powerful oxidative reactions. In general, a decrease in glutathione levels is a normal response to exposure to oxidative stress and oxidative stress, and this could be part of the body's mechanism to cope with oxidative stress [21].

The reason for the decrease in glutathione levels in a group exposed to both gabapentin and hydrogen peroxide may be the result of a common oxidative reaction between Gabapentin and intracellular hydrogen peroxide. Glutathione acts as an important antioxidant that protects cells from damage resulting from oxidative reactions. When cells are exposed to gabapentin and hydrogen peroxide, An oxidative reaction may occur leading to the consumption of glutathione as it attempts to interact with the oxidized molecules generated by the reaction between gabapentin and hydrogen peroxide[22]

This oxidative reaction can lead to a reduction in glutathione levels within the cell. Additionally, an interaction between gabapentin and hydrogen peroxide can produce reactive compounds that consume glutathione or affect its metabolism, contributing to its lower levels [23].

Conclusions

1- There is a harmful synergistic interaction between hydrogen peroxide and gabapentin in chicken chicks.

2- Hydrogen peroxide, alone or with gabapentin, modulates the normal physiological function of the neurotransmitters kappa and glutamate in chicken chicks.

3- Hydrogen peroxide, alone or with gabapentin, modulates the normal physiological function of the antioxidants malondialdehyde and glutathione in chicken chicks.

4- There is a harmful synergistic interaction between hydrogen peroxide and gabapentin in chicken chicks.

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تأثير تآزري للكابابنتين مع بيروكسيد الهيدروجين على الناقلات العصبية ومضادات الأكسدة في فراخ الدجاج

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الملخص

المكان الذي أجريت فيه التجربة هو بيت الحيواني في جامعة تكريت وكانت المدة 30 يوما وكان عدد الطيور المستخدمة في التجربة 60 طائر وتراوحت أوزانها بين 75 غرام – 110 غرام. كما أن جرعة الكابابنتين المستخدمة كانت 990 ملغم/كغم.

كان الهدف من هذه الدراسة هو معرفة تأثير الاجهاد التأكسدي المحدث ببيروكسيد الهدروجين على الاستجابة الدوائية للكابابنتين ومقارنة هذا التأثير مع الافراخ الطبيعية فضلا عن معرفة تأثير الاجهاد التأكسدي على النواقل العصبية (الكابا والكلوتاميت)، ومضادات الاكسدة (المالون ثنائي الالديهايد والكلوتاثايون)..

وعمل إعطاء بيروكسيد الهدروجين على احداث الاجهاد التأكسدي في افراخ الدجاج وبصورة معنوية من خلال الزيادة المعنوية في تركيز المالون ثنائي الالديهايد والانخفاض المعنوي في تركيز الكلوتاثيون فضلا عن ان إعطاء الكابابنتين زاد من هذا التأثير في أفراخ الدجاج المجهدة مقارنة مع الافراخ الطبيعية .

عمل إعطاء الكابابنتين على زيادة في الناقل العصبي الكابا وبصورة معنوية مع الإبقاء على تركيز الكلوتاميت مقاربا لمجموعة السيطرة السالبة بينما سبب بيروكسيد الهدروجين الزيادة في تركيز كلا النواقل العصبية الكابا والكلوتاميت فضلا عن إعطاء الكابابنتين وبيروكسيد الهدروجين قد عملا معا على زيادة المعنوية المفرطة لكلا من الكابا والكلوتاميت.

نستنتج من هذه الدراسة ان الاجهاد التأكسدي المحدث ببيروكسيد الهدروجين في افراخ الدجاج عمل على حدوث زيادة في الفعالية الدوائية للكابابنتين فضلا عن حدوث تأثيرات سمية ضارة على مستوى النواقل العصبية ومضادات الاكسدة.