The Effect of Oxytocin and Some Chemicals in a Rat Model of Absence Epilepsy (WAG/Rij)

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Abstract

Absence epilepsy characterized by sudden and brief unconsciousness is a form of idiopathic generalized epilepsy that occurs in childhood. In this study, 104 Wag/Rij male rats were used. Animals were divided into 13 groups, oxytocine 80 nmol/kg, valproic acid 300 mg/kg, ethosuximide 200 mg/kg, magnesium sulfate 600 mg/kg, methylprednisolone 20 mg/kg and double-triple combination of these chemicals were intraperitoneally given to the groups. In all one drug administered groups, we recorded significant decrease in mean SWD. In addition to this, we observed a stronger reduction in mean SWD when the drugs were combined with oxytocine in double combination groups. For triple combination groups, when methylprednisolone was added to the groups, larger changes were seen in mean SWD (p<0.05). We conclude that oxytocine decrease the number of absence seizures, and the combination of oxytocin with other drugs increase anti-epileptic effects of the drugs.

Keywords: Wag/Rij; Oxytocine; Ethosuximide; Valproic acid; Methylprednisolone; Magnesium sulfate

Introduction

Epilepsy is one of the most important diseases of central nervous system (CNS) and observed in approximately 1% of the world population [1]. Although epilepsy is usually characterized by convulsive seizures, it may arise at other clinical manifestations such as the absence depending on the brain region affected [2]. Epilepsy is defined as short paroxysmal disorder of brain function. Epilepsy is observed as seizures with sudden, abnormal and hyper-synchronized discharge of a group of neurons [3]. Seizures can be partial or generalized, depending on the starting location and spread of abnormal neuronal discharge. While the reasons of partial seizures are usually tumor, trauma etc. (secondary epilepsy), generalized seizures are not related to a specific cause (primary, idiopathic form). The two common forms of generalized epilepsy are tonic-clonic (grand mal) and absence (petit mal) [4].

The mechanism causing the formation of epileptogenesis is not well known. However, in this regard, several mechanisms such as certain non-synaptic events, cell loss, altered receptor construction, anatomical changes at the cellular level, presynaptic ending overstimulation and incorrect synaptogenesis are suggested [4,5]. As the underlying pathophysiological mechanism of epilepsy is not exactly known, current treatment approach is suppression of seizures with anticonvulsant drugs [5]. In order to elucidate the molecular mechanisms underlying epilepsy, a variety of experimental models were improved and the effect of many chemical agents on epileptic activity has been investigated. Many of the researchers suggest that the excessive amount of Ca++ ion entry into cells play a role in the formation of epileptic activity [6]. To determine the role of ion channels in the pathogenesis of epilepsy and the association with sudden cardiac death due to long QT syndrome in some patients with epilepsy has drawn attention to this issue. The increase in QT in patients with epilepsy is thought to be due to two reasons; genetic mutations that cause ion channel disorders and autonomic dysfunction. The heart rate variability and blood pressure abnormalities during seizures in patients with epilepsy are indicators of autonomic dysfunction [7].

The symptomatic and idiopathic epilepsies are the main forms of the disease. The idiopathic epilepsy detected without a brain lesion is characterized by recurrent focal or generalized seizures. The typical absence epilepsy is located within idiopathic generalized epilepsy group, is a generalized epilepsy form characterized by sudden and short-term loss of consciousness accompanied by EEG 2.5-4 Hz bilateral and symmetrical thorn-and-wave discharges (DDD). The thalamo-cortical structures are responsible for the formation of DDD, a phenomenon of the typical absence epilepsy that accounts for approximately 4% of childhood seizures [8]. The neurochemical basis of abnormal neuronal discharge is unclear. The increased excitatory (stimuli) amino acid transmission (e.g., glutamate), reduced the transmission of inhibitor (repressor) (e.g., GABA) amino acid...
transmission or the abnormal electrical properties of the affected cells may be responsible for the pathophysiology [9]. There are few ways for preclinical evaluation of antiepileptic drugs such as maximal electroconvulsive shock, pentylenetetrazol (leptazol) induced seizures and many animal models [9]. The diversity and prevalence of experimental models of absence epilepsy have greatly contributed to the understanding of the mechanism underlying the seizure type, the development of therapeutic approaches and allows examination of the interaction of different types of seizures. The genetic animal model of absence epilepsy (WAG/Rij and GAERS strains) illustrates the clinical, pharmacological, EEG properties of absence epilepsy [10].

Oxytocin (Ox) is a peptide hormone comprising 9 amino acids. Oxytocin is a neurohypophysial nonapeptide synthesized in the paraventricular and supraoptical nuclei of the hypothalamus and plays a role in lactation and parturition [11]. Oxytocin is one of the most studied research topic at last decade. It was found to exert some neuroprotective effects in the lactating women [12]. It is also known to have anxiolytic effects of behavioral studies, but the effect level cannot be explained fully. In the studies, it has been shown that oxytocine eliminates amygdala EEG activity formed by the injection anxiety. Oxytocine suppresses awake spontaneous amygdala EEG in rats and improves nerve conduction velocity in experimental diabetic peripheral neuropathy has been shown. These findings suggest that oxytocine shows its effect via the inhibitory pathway like a VIP and probably some other peptides in brain and brainstem [13]. Some of the previous studies showed that oxytocine suppressed the frequency increment and spike wave complexes as dose-dependent in thalamic EEG results formed by PTZ suppression. Some others showed oxytocine to be a new candidate agent can be used in epilepsy treatment [13].

We mainly aimed to investigate whether oxytocin exhibited an anticonvulsant effect using EEG recordings of genetic animal model of absence epilepsy. Oxytocin has been shown to affect pentylenetetrazol-induced seizures [13]. Thus we prefer a genetic animal model of absence epilepsy. In this study, we aimed to search the antiepileptic properties of oxytocine by combining two major antiepileptic drugs (valproic acid, ethosuximide), magnesium sulfate anticonvulsants and methylprednisolone synthetic corticosteroid.

Materials and Methods

Experimental animals

The present study was performed in Cumhuriyet University Animal Laboratory after approval of Local Ethics Committee. Healthy adult male, weighing 250-300 g, genetic animal model of absence epilepsy Wag/Rij rats (n=104) were used. All animals were fed by a standard laboratory diet and they could drink water whenever they requested. Rats were capable of normal activity in the cages, 22 ± 2°C, humidity (50-70%) and 12 hours of night/day. All animals were kept under observation for a few days before the study to decide if they are healthy or not.

Experimental procedure

In the present study, oxytocine peptide hormone, valproic acid and ethosuximide antiepileptic drugs, methylprednisolone corticosteroid and magnesium sulfate mineral were used. The dose was determined according to the literature discussed previously.

1. Group baseline records were taken without drug administrated. 2. Group after baseline recordings oxytocine (Ox) at the amount of 80 nmol/kg intraperitoneal (ip) applied [13]. 3. Group after the basal recordings, methylprednisolone (MP) at the amount of 20 mg/kg ip applied [14]. 4. Group after the basal recordings valproic acid (VPA) at the amount of 300 mg/kg ip applied [15]. 5. Group after the basal recordings magnesium sulfate (Mg) at the amount of 600 mg/kg ip applied [16]. 6. Group after baseline recordings ethosuximide (ETH) amount of 300 mg/kg ip applied [17].

In the combined group; 7 Group after baseline recordings first Ox (80 nmol/kg ip) and then magnesium sulfate (600 mg/kg/ip) were applied. 8. Group after baseline recordings first Ox (80 nmol/kg ip), then valproic acid (300 mg/kg/ip) were applied. 9. Group after the baseline recordings first Ox (80 nmol/kg/ip), then methylprednisolone (20 mg/kg/ip) were administered. 10. Group after baseline recordings first Ox (80 nmol/kg/ip), then ethosuximide (300 mg/kg/ip) were applied. 11. Group after baseline recordings first Ox (80 nmol/kg/ip) and methylprednisolone (20 mg/kg/ip) then the valproic acid (300 mg/kg/ip) were applied. 12. Group after baseline recordings first Ox (80 nmol kg/ip) and methylprednisolone (20 mg/kg/ip), then the ethosuximide (300 mg/kg/ip) were applied. 13. Group after baseline recordings first Ox (80 nmol/kg/ip) and methylprednisolone (20 mg/kg/ip), then the magnesium sulfate (600 mg/kg/ip) were applied.

Stereotactic application

Before stereotactic application, animals were anesthetized with ketamine 90 mg/kg IM+Xylazine at 3 mg/kg intramuscular (im) or subcutaneous (sc). After checking the depth of anesthesia with the corneal and claw reflexes, stereotactic instrument is positioned to bregma and lambda points in the same plane. The heads of the rat are fixed to the stereotactic instrument through stabilizer bars tool from ear hole and the front teeth, then shaved the hairs on the scalp, and lambda and bregma point were uncovered by opening the incision in the midline of the skull bones. All electrode screws are placed using rat brain atlas by Paxinos & Watson and bregma is the reference point "0". 4 units hole in 1 mm diameter were opened by using a tour engine. Two bipolar EEG deep implant (screw) on parietal bone over and the other two screws on frontal bone were placed so as to contact with the cerebral cortex. Frontal region 2 (AP=2, L= ± 2.5) and the parietal region 2 (AP=6=2, L= ± 2.5). The electrodes were fixed to the skull with the help of dental acrylic. After surgical procedures, animals were put in separate cages and general conditions of the animals were followed for 1-week rest period.
EEG records

Before starting work, animals were randomly divided into 13 groups. Number of rats in each group and drugs are shown in Table 1. Animals in each group were held on Neuropsychology laboratory of Department of Physiology, Cumhuriyet University Faculty of Medicine for 2 hours. This provides adaptation of the rats to the environment. Then, animals were put in the Plexiglas cages during experiments and the records were taken using the head connectors and cables through EEG recording system (PowerLab 4S, AD Instruments, UK). When the interference was not seen, record storage was started. First record was continued for 2 hours. Then, drug administrations were performed according to the groups and after 5 minutes second EEG again was stored for 2 hours. EEG signal was amplified and filtered at 1 and 100 Hz. EEG recordings were stored on the computer and then were analyzed by the program called "Chart for Windows" EEG recordings were conducted in the laboratory of Department of Physiology of School of Medicine of Cumhuriyet University.

Table 1 Experimental groups in the present study.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Short form</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Control</td>
<td>C</td>
<td>8</td>
</tr>
<tr>
<td>2 Oxytocine</td>
<td>Ox</td>
<td>8</td>
</tr>
<tr>
<td>3 Methylprednisolone</td>
<td>MP</td>
<td>8</td>
</tr>
<tr>
<td>4 Valproic acid</td>
<td>VPA</td>
<td>8</td>
</tr>
<tr>
<td>5 Magnesium sulfate</td>
<td>Mg</td>
<td>8</td>
</tr>
<tr>
<td>6 Ethosuximide</td>
<td>ETH</td>
<td>8</td>
</tr>
<tr>
<td>7 Oxytocine+Magnesium sulfate</td>
<td>Ox+Mg</td>
<td>8</td>
</tr>
<tr>
<td>8 Oxytocine+Valproic acid</td>
<td>Ox+VPA</td>
<td>8</td>
</tr>
<tr>
<td>9 Oxytocine+Methylprednisolone</td>
<td>Ox+MP</td>
<td>8</td>
</tr>
<tr>
<td>10 Oxytocine+Ethosuximide</td>
<td>Ox+ETH</td>
<td>8</td>
</tr>
<tr>
<td>11 Oxytocine+Methylprednisolone+Valproic acid</td>
<td>Ox+MP+VPA</td>
<td>8</td>
</tr>
<tr>
<td>12 Oxytocine+Methylprednisolone+Ethosuximide</td>
<td>Ox+MP+ETH</td>
<td>8</td>
</tr>
<tr>
<td>13 Oxytocine+Methylprednisolone+Magnesium sulfate</td>
<td>Ox+MP+Mg</td>
<td>8</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>104</td>
</tr>
</tbody>
</table>

Evaluation of spike and wave discharges (SWD)

SWD observed in WAG/Rij strain rats was determined visually from EEG and average spike and the duration of wave discharges for each group were calculated by using 2 hours record after drug administration and 2 hours for baseline. Average time was evaluated by using the ratio of the duration of cumulative thorns and wave discharges (tSWD) to the number of thorns and wave discharges (nSWD). High amplitude asymmetric synchronized rhythmic activity consisting of spike and wave period of at least 2 seconds were considered as SWD’s criterion [18].

Statistical analysis

Statistical evaluation of the data was performed using software package "SPSS for Windows 22.0". Kruskal-Wallis for comparing the level of the entire group, the Mann-Whitney U test to determine the differences and the Wilcoxon rank test for intra-group comparisons were used. P<0.05 was considered as significant.

Results

There was statistically significant difference between the after values of mSWD and the before mSWD values in all groups (Table 2). Accordingly, Ox, MP, Ox+MP compared to the after mSWD values with the before mSWD values of the groups were determined to be significantly different (Figure 1). Accordingly, Ox, VPA, OT+VPA compared to the after mSWD values with the before mSWD values of the groups were determined to be significantly different (Figure 2). Accordingly, Ox, Eth, OT+ETH compared to the after mSWD values with the before mSWD values of the groups were determined to be significantly different (Figure 3). Accordingly, Ox, ETH, OT+ETH compared to the after mSWD values with the before mSWD values of the groups were determined to be significantly different (Figure 4). Accordingly, Ox, MP, ETH, Ox+MP+ETH compared to the after mSWD values with the before mSWD values of the groups were determined to be significantly different (Figure 5). Accordingly, Ox, MP, VPA, Ox+MP+VPA compared to the after mSWD values with the before mSWD values of the groups were determined to be significantly different (Figure 6). Accordingly, Ox, MP, Mg, Ox +MP+Mg compared to the after mSWD values with the before mSWD values of the groups were determined to be significantly different (Figure 7).

Table 2 Mean of spike and wave discharges values before and after drug application.

<table>
<thead>
<tr>
<th></th>
<th>Before mSWD</th>
<th>After mSWD</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (C)</td>
<td>8.2 (8.1 – 8.3)</td>
<td>8.2 (8.1 - 8.3)²</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Oxytocine (Ox)</td>
<td>8.2 (7.2 – 9.1)</td>
<td>5.9 (5.1 - 6.2)³</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Methylprednisolone (MP)</td>
<td>8.1 (6.0 – 10.1)</td>
<td>6.6 (5.4 - 7.5)²</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Valproic acid (VPA)</td>
<td>8.1 (6.5 – 10.7)</td>
<td>4.9 (4.2 - 5.8)³</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Magnesium sulfate (Mg)</td>
<td>8.2 (6.8 – 10.1)</td>
<td>6.8 (6.2 - 7.4)²</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Drug Combination</td>
<td>Spike Discharge Before (μV)</td>
<td>Spike Discharge After (μV)</td>
<td>p Value</td>
</tr>
<tr>
<td>------------------</td>
<td>-----------------------------</td>
<td>---------------------------</td>
<td>---------</td>
</tr>
<tr>
<td>Ethosuximide (ETH)</td>
<td>8.3 (7.2 - 10.2)</td>
<td>4.8 (3.9 - 5.6)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Ox + Mg</td>
<td>8.2 (6.2 - 10.2)</td>
<td>5.6 (4.5 - 6.2)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Ox + VPA</td>
<td>8.3 (6.0 - 10.2)</td>
<td>4.8 (3.9 - 5.7)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Ox + MP</td>
<td>8.3 (7.4 - 9.6)</td>
<td>5.5 (5.2 - 6.2)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Ox + ETH</td>
<td>8.3 (8.3 - 10.3)</td>
<td>4.6 (3.6 - 5.6)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Ox + MP + VPA</td>
<td>8.3 (7.4 - 9.4)</td>
<td>4.6 (4.1 - 5.6)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Ox + MP + ETH</td>
<td>8.4 (6.4 - 10.1)</td>
<td>4.5 (4.1 - 4.8)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Ox + MP + Mg</td>
<td>8.3 (6.2 - 10.2)</td>
<td>5.5 (5.0 - 5.6)</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

a| Control, MP, VA, ESM, OT + MGS, OT + VA, OT + MP, OT + ESM, OT + MP + VA, OT + MP + ESM were compared.
b| Control, MP, VA, ESM, OT + MGS, OT + MP, OT + VA, OT + MP + ESM were compared.
c| Control, OT, VA, ESM, OT + MGS, OT + VA, OT + MP, OT + ESM, OT + MP + VA, OT + MP + ESM were compared.
d| Control, OT, MP, VA, OT + MGS were compared.
e| Control, OT, VA, MGS, OT + MGS, OT + VA, OT + MP, OT + ESM, OT + MP + VA, OT + MP + ESM were compared.
f| Control, MT, VA, ESM, OT + MGS, OT + VA, OT + MP, OT + ESM, OT + MP + VA, OT + MP + ESM were compared.
g| Control, MT, VA, ESM, OT + MGS, OT + VA, OT + MP + VA, OT + MP + ESM were compared.
h| Control, MT, VA, MGS, OT + MGS, OT + VA, OT + MP, OT + ESM, OT + MP + VA, OT + MP + ESM were compared.
i| Control, MT, VA, ESM, OT + MGS, OT + MP, OT + MP + VA, OT + MP + ESM were compared.
j| Control, MT, VA, MGS, OT + MGS, OT + VA, OT + MP, OT + ESM, OT + MP + VA, OT + MP + ESM were compared.
k| Control, MT, VA, ESM, OT + MGS, OT + MP, OT + MP + VA, OT + MP + ESM were compared.
l| Control, MT, VA, MGS, OT + MGS, OT + VA, OT + MP, OT + ESM, OT + MP + VA, OT + MP + ESM were compared.

**Figure 1** The mean of spike and wave discharges of oxytocin and methylprednisolone groups values before and after drug application (before and after mSWD). *p<0.05 (compared to before mSWD value of same group).

**Figure 2** The mean of spike and wave discharges of oxytocin and valproic acid groups values before and after drug application (before and after mSWD). *p<0.05 (compared to before mSWD value of same group).

**Figure 3** The mean of spike and wave discharges of oxytocin and magnesium groups values before and after drug application (before and after mSWD). *p<0.05 (compared to before mSWD value of same group).

**Figure 4** The mean of spike and wave discharges of oxytocin and ethosuximide groups values before and after drug application (before and after mSWD). *p<0.05 (compared to before mSWD value of same group).
Discussion

We recorded that oxytocin decreased the mean of absence seizures. Oxytocin augmented anti-epileptic effects of Ethosuximide and Valproic acid. The addition of Methylprednisolone functioned as a promoter on oxytocin combinations. We evaluated the effects of double-triple combination of drugs. For this reasons, mean spike wave discharges (mSWD) in the groups were considered. When mean spike discharge (tSWD/nSWD) was considered, agents used all taken into account; oxytocin, ethosuximide, valproic acid, methylprednisolone and magnesium sulfate were effective. The maximum effect was performed by ethosuximide. Valproic acid was effective as much as ethosuximide. Oxytocin and methylprednisolone decreased the mSWD value. The minimum effect was performed by magnesium sulfate. Van Rijn et al. [19] indicated that ethosuximide application on WAG/Rij rats provided decreasing effect on mSWD value. Clementina et al. [19] indicated that mSWD value was decreased in ESM applied absence epileptic rats. Mathew et al indicated that mSWD value of seizure Wistar created by Pentylenetetrazole (PTZ) was decreased by ethosuximide application. In this research, ethosuximide decreased mSWD value and when agents used all taken into account, it was the most effective. We thought that it provided this by blocking Ca channels, especially T type Ca channels. Van Rijn et al. [19] indicated that valproic acid application on WAG/Rij rats provided decreasing effect on mSWD value. Glauser et al. [20] indicate that prolonged use of valproic acid on 128 patients with absence epilepsy provided higher activity. Our study in parallel with most of the studies in the literature indicated that valproic acid application provided decreasing effect on mSWD value. We thought that it provided this by inhibiting GABA transaminase that cause increase in GABA level and this event provide antiepileptic effects. Erbaş et al. [13] reported that oxytocin reduce the increased mSWD in EEG activity due to injection anxiety. Also Erbaş et al. recorded that oxytocin reduce the PTZ induced mSWD depending on dose in the thalamic EEG. In the present study, oxytocin reduced the mDD values as other anti-epileptic drugs (valproic acid, ethosuximide). This effect of oxytocin, suggests that it acts through brain stem inhibitory pathways like VIP and some other peptides. Willmore et al. [14] investigated the effect of corticosteroids on epileptic seizures in their study and results demonstrated that methylprednisolone decreased the mSWD value. Most research in literature as parallel as in our study, methylprednisolone shows detractive impact on mSWD’s rate. We thought that this effect (it was indicated in the previous studies) was provided by increasing GABA level that causes antiepileptic effect. Magnesium sulfate is a widely used anticonvulsant in preeclampsia and eclampsia that are one of the most important causes of maternal and fetal morbidity and mortality [21]. Sibai [21] indicates that magnesium sulfate decreased the mSWD value. Oliveira et al. [22] indicate that magnesium sulfate decreased the mSWD value as dose dependent. Our study in parallel with most of the studies in the literature indicated that magnesium sulfate decreased the mSWD. When agents used are all taken into account, it provides the most minimum effect. We thought that this effect (it was indicated in the previous studies) was provided by the indirect
effect of glutamate antagonism increasing GABA level that causes antiepileptic effect. Especially the anticonvulsant effect of combination of magnesium sulfate and oxytocin should be investigated in the preeclamptic animal models. When oxytocin was combined with valproic acid, ethosuximide, magnesium sulfate and methylprednisolone as binary combined groups, it decreased mSWD value in all binary combined groups. The best decreased in mSWD value was detected in oxytocin+ethosuximide group. The least decreased in mSWD value was detected in oxytocin+magnesium group. Belozertsev et al. [23] reported that magnesium sulfate and gabapentin produce weak effect on the number of mSWD, and lamotrigine, topiramate, and sodium valproate had severe effect on it. In triple combined groups, the best decreased in mSWD value was detected in oxytocin+methylprednisolone+ethosuximide group. Methylprednisolone provides same effect on oxytocin+valproic acid group. But, methylprednisolone did not provide same effect on oxytocin+magnesium sulfate group. Oxytocin was more effective on binary combined groups. In triple combined groups, methylprednisolone with oxytocin increased the effect of ethosuximide. Methylprednisolone was not so effective when it was combined with oxytocin. However, when methylprednisolone was combined with oxytocin+ethosuximide, it decreased the mSWD value significantly. It provided same effect on oxytocin+valproic acid combined group.

When the literature is reviewed, we saw no study about oxytocin combined with corticosteroids and antiepileptic. Consequently, the present study is the first one about the effects of the combination of oxytocin, corticosteroid and antiepileptic. Further studies are needed to be performed in the female or pregnant experimental animals and preeclamptic animal models in order to evaluate the effect of combination of oxytocin and magnesium sulfate in the prophylaxis of seizure.

Conclusion

In conclusion, our study aimed to search the antiepileptic properties of oxytocin by combining two major antiepileptic drugs (valproic acid, ethosuximide), magnesium sulfate anticonvulsants, methylprednisolone and synthetic corticosteroid. Oxytocin caused a decrease in number of absence seizures, and the combination of oxytocin with other drugs increase anti-epileptic effects of the drugs. The addition of MP to oxytocin combinations increased anti-epileptic effects of the combinations more. However, further studies must be performed to determine the genetic effects of the oxytocin.

References