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The Effect of Gestational Exposure of Sodium Cromoglycate on Epileptiform Activities in the Rat Offspring

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Abstract:

BACKGROUND: Epilepsy is one of the most common neurological diseases globally. Mast cells are known to be the main source of brain histamine, which is identified as being involved in seizure modulation. Sodium cromoglycate is a popular mast cell stabilizer and is proposed as the first line therapy in chronic asthma and systemic mastocytosis. Considering the importance of gestational period in brain formation and given the apparent role of the histaminergic system in developmental stages, the question arises as to whether gestational exposure to sodium cromoglycate can impact epileptic susceptibility in the offspring.

OBJECTIVES: The aim of this study was to evaluate the effects of gestational exposure of sodium cromoglycate on pentylenetetrazole-induced epileptiform activities in the rat offspring.

METHODS: Twelve pregnant Wistar rats were divided into 3 groups (n=4) including: two treatment groups which received intraperitoneal Sodium cromoglycate in doses of 25 and 50 mg/kg once daily at the last week of pregnancy, and the control group which only received Phosphate-buffered saline at the same amount (0.5 ml) and the same order. At postnatal day 12, eight male pups were selected from each group's offspring. Anesthetized pups were transferred to stereotaxic frame and silver electrodes were implanted surgically over the brain cortex. After recovery, pups were placed into the recording chamber and pentylenetetrazole-induced epileptiform activities were measured.

RESULTS: Electrographic data showed a decrement in seizure latency and increment in frequency/amplitude of the spikes in sodium cromoglycate groups in comparison to the control group ($p<0.05$). Also, Parallel behavioral observations were consistent with the electrographic data.

CONCLUSIONS: The obtained results reveal enhanced epileptiform activity in developing rats due to prenatal exposure to sodium cromoglycate.

Keywords:

Epileptiform activity, Gestational exposure, Offspring, Rat, Sodium cromoglycate

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Introduction

Today it is well proven that not only genetic and postnatal environment, but also prenatal events can highly impact the future of the fetus (Bercum, Rodgers et al. 2015; Kim and Leventhal 2015). Prenatal exposure of various substances can alter brain function through modifying neuronal excitability (Naseer, Shupeng et al. 2009; Fueta, Sekino et al. 2018). There is a spectrum of pathological manifestations caused by alteration in neuronal excitability, among which epilepsy is considered as the most prevalent one (Camp, 2012).

Epilepsy is a neurological condition that occurs due to abnormal electrical firing in cerebral neurons leading to variant symptoms such as sudden loss of consciousness, muscular spasm and sensational or behavioral changes in an individual (Brodie, Besag et al. 2016). Fifty million people worldwide suffer epilepsy, making it one of the most common neurological diseases globally (Fiest, Sauro et al. 2017). The mortality rate in suffering individuals is three times higher due to a spectrum of subsequent conditions such as suicide, trauma, driving accidents and sudden unexpected death in epilepsy (SUDEP) (Gaitatzis and Sander, 2004).

The exact pathogenesis of epilepsy is unclear but the impairment of brain stimulant and/or inhibitory neurotransmitters (GABA and Glutamate), is often referred to explain the etiology (Yuan, Low et al. 2015). More recently participation of histaminergic system in modulation of epilepsy is introduced and the protective role of brain histamine against epileptic seizures is demonstrated (Kukko-Lukjanov, Lintunen et al. 2010; Bhowmik, Khanam et al. 2012). In contrast, H1 receptor blockers have the potential to increase epileptogenicity (Fujii, et al. 2003; Zolaly, 2012). Interestingly the epileptogenic effect of H1 receptor blockers is more pronounced during developmental period (Yokoyama and Iinuma, 1996).

The main sources of brain histamine are mast cells and histaminergic neurons, while mast cells hold a larger share (Chikahisa, Kodama et al. 2013). Mast cells association with immune responses and allergic reactions has long been recognized (Frenzel and Hermine 2013; St John and Abraham 2013). When it comes to allergic reactions, mast cell stabilizing agents are commonly used therapeutics to prevent histamine release (Chang and Shiung 2006; Finn and Walsh 2013). Similar to H1 receptor blockers, some mast cell stabilizers are also proved to have epileptogenic effects (Yamada, et al. 2012; Yokoyama, et al. 2012).

Sodium cromoglycate (Cromolyn) is one of the most popular mast cell stabilizers which is proposed as the first line therapy in chronic asthma (Shapiro and Konig, 1985; Murphy and Kelly, 1987) and is referred to as one of the mainstays in the treatment of systemic mastocytosis (Soter, et al. 1979; Liberman, et al. 1980; Horan, et al. 1990). Considering the importance of gestational period in brain formation and given the epileptogenic effect of antihistamine and/or mast-cell stabilizer agents in the developmental period (Yokoyama and Iinuma, 1996), the question arises as to whether gestational exposure to cromolyn can impact epileptic susceptibility in the offspring. Also, it is worth mentioning that despite abundant application of cromolyn in various therapeutic purposes there is still lack of sufficient information about its gesta-

tional exposure and the following postnatal outcomes. Therefore, the current study was designed to evaluate the effects of gestational exposure of cromolyn on pentylenetetrazole-induced epileptiform activities in the rat offspring.

Material and Methods

Animals: Pregnant Wistar rats were bred under standard conditions in basic sciences department animal house. Vaginal examination was performed at 7:00 am on the next day after mating and females with the vaginal plug were defined as gestational day 0. During pregnancy, they were housed individually under temperature-control (24±2 ºC) and 12-h light-dark cycle with free access to laboratory chow and water. All surgical and experimental procedures were performed in accordance with the University Ethics Committee.

Groups

Pregnant animals were randomly divided into three groups (n=4 in each):

Group 1: pregnant animals were intraperitoneally (IP) administered with 0.5 ml Phosphate-buffered saline once daily and considered as control.

Group 2: pregnant animals were intraperitoneally (IP) administered with 25 mg/kg/day cromolyn from 15th day until the end of pregnancy.

Group 3: pregnant animals were intraperitoneally (IP) administered with 50 mg/kg/day cromolyn from 15th day until the end of pregnancy.

In all groups, last gestational day was considered for the materials exposure (day 15 to the end of pregnancy).

Drugs and chemicals: Materials used in this study (Sodium cromoglycate, Pentylenetetrazole and Phosphate-buffered saline as solvent) were purchased from Sigma-Aldrich (Chemical Co. Germany).

Surgical procedure: At postnatal day 12 (PN12), eight male pups were randomly selected from each group's offspring. A combination of ketamine/xylazine (Alfasan, Holland), (50/7 mg/kg, IP) was used for anesthesia induction and loss of toe pinch reflex considered as the sufficient level of anesthesia. Anesthetized pups were transferred to stereotaxic frame and the ear bar tips were placed in the auditory canal. Animals were kept warm by setting temperature-controlled unit (NARCO Bio-System, USA) to 37 °C and if needed, lubricating ointment was applied to the eyes.

Sterile incision was made on the scalp along the midline and after exposing the skull, four burr holes were drilled at the following locations: two symmetrical holes over the frontal cortex (0.5 mm anterior to the bregma and 3.0 mm lateral to the midsagittal suture) and two other holes posterior to lambda for the reference and ground electrodes (Criado, et al. 2012; Garcia-Cabrero, et al. 2012).

Silver electrodes were placed through the burr holes to settle between the dura and the skull and sealed with small amounts of cyanoacrylate gel. Electrodes were then soldered to miniature receptacles, and the whole assembly was secured in the skull with acrylic cement. The pups were allowed to completely recover from anesthesia and then returned to the dam.

Electrographic/ Behavioral measurements: Two days after surgical recovery (PN14), pups were placed into the recording chamber. Before the experiments began, flexible lightweight cables were attached to the implanted miniature connector that

allowed the rat's unrestricted movement during the recording. For inducing seizure in the pups they were intraperitoneally injected with 50 mg/kg Pentylenetetrazole (PTZ) (Puig-Lagunes, Manzo et al. 2016) and electrographic/behavioral measurements were obtained.

Electroencephalographic (EEG) recording: The EEG signal was recorded with a physiograph (NARCO Bio-System, USA) via a universal coupler (Universal coupler, type 7189, NARCO Bio-systems, USA) and the data were transferred to PowerLab data acquisition system (AD Instruments- Australia) and analyzed using Labchart7 software.

An electrographic seizure was defined as a high-frequency (>5 Hz) and high amplitude (twice larger than the baseline) discharge that lasted for at least 10 sec (Ndode-Ekane and Pitkanen 2013).

For evaluating electrographic seizures, as described previously seizure latency (the time interval between PTZ injections to the appearance of the first electrographic seizure), spike frequency (number of spikes per minute) at 15th min after PTZ injection, and spike amplitude (μv) during epilepsy episodes were calculated (Anschel, et al. 2004).

Behavioral testing: During EEG recording concurrent video was also captured for evaluation of behavioral changes and helping excluding electrical noises (White, et al. 2006). Seizures were scored based on behavior and EEG findings using a modified Racine's scale (Luttjohann, et al. 2009) (Table 1). Spikes and sharp waves were considered to represent seizure activity only when they were associated with abnormal behaviors that were confirmed on video monitoring. This scoring system was used for evaluation of seizure activity for 30 min after PTZ injection.

Statistical analysis: Statistical comparisons were performed using the GraphPadprismTM version 7.00 (GraphPad, San Diego, CA, USA). The nonparametric data were analyzed using Kruskal-Wallis analysis and parametric data were analyzed using one-way analysis of variance (one-way ANOVA). When significant differences were obtained, post-hoc comparisons within logical sets of means were performed using Tukey's test. Data were summarized as mean ± SD. P values less than 0.05 were considered statistically significant.

Results

Behavioral seizures: As shown in Fig.1, behavioral signs of seizures were observed in pups within 30 min after PTZ injection. Cromolyn with doses 25 and 50 mg/kg/day

Table 1. Modified Racine's scale (Luttjohann, et al. 2009).

Score	Behavioral stage	EEG findings
0	No change in behavior	Baseline
1	Sudden behavioral arrest, motionless staring (with orofacial automatism)	High amplitude activity/slow waves
2	Head nodding, Stiff tail	Spikes, sharp waves
3	Forelimb clonus with lordotic posture	Spikes or polyspikes, sharp waves
4	Forelimb clonus, with rearing and falling	Spike bursts/spike and wave discharges
5	Generalized tonic-clonic activity with loss of postural tone, often resulting in death, wild jumping	Spike bursts/spike and wave discharges
6	Death	No electrical activity

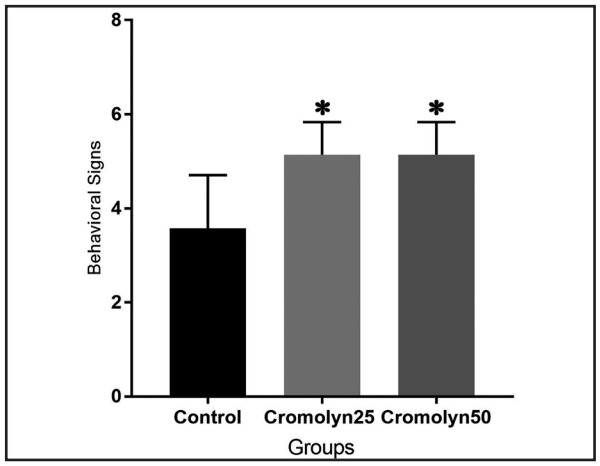

Figure 1. Effect of PTZ in inducing seizure behaviors in freely moving pups. Histograms showing Racine score behavior of the animals in control (n=8), Cromolyn25 mg/kg/day (n=8) and Cromolyn 50 mg/kg/day (n=8).* P<0.05.

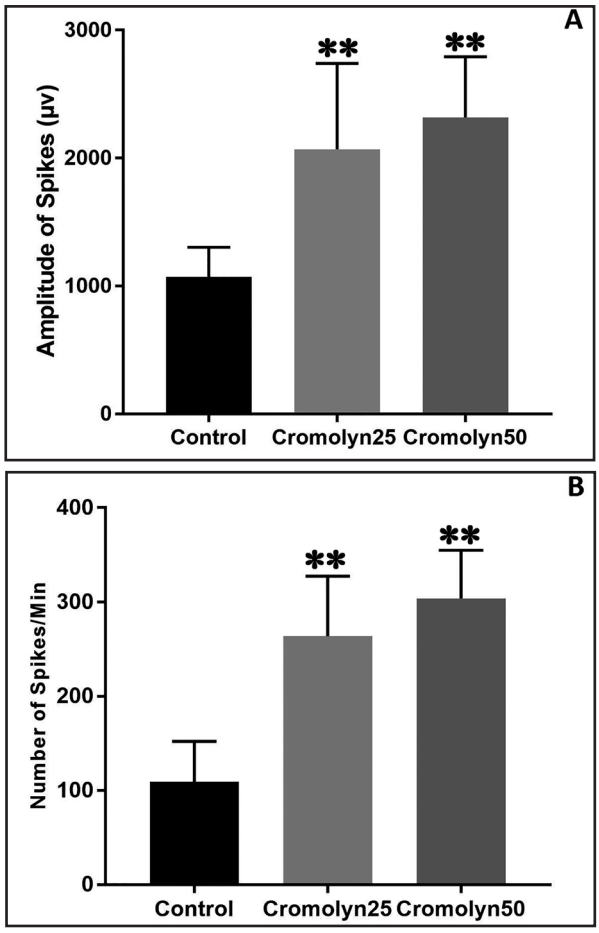

Figure 2. A, the amplitude of spike waves induced by PTZ in pups. B, the number of spike waves induced by PTZ in pups in control (n=8), Cromolyn25 mg/kg/day (n=8) and Cromolyn 50 mg/kg/day (n=8). ** P<0.01.

significantly increased PTZ-induced seizure behaviors in comparison to the control group in freely moving pups (P<0.05). However, there was no significant difference between 25 and 50 mg/kg/day of cromolyn groups (P>0.05). Behavioral signs score in different groups were: control: 3.57 ± 1.1; cromolyn (25 mg/kg/day): 5.14 ± 0.7 and cromolyn (50 mg/kg/day): 5.28 ± 0.6.

Electrographic seizures: In Fig. 2, the effects of prenatal injection of cromolyn on the number and amplitude of spike waves induced by PTZ is shown. In different groups (control, cromolyn 25 mg/kg/day and 50 mg/kg/day) the numbers of spikes/min were 109.14±41.9; 263.57±73 and 303.42±41.4 at the 15th minute, respectively. According to results, cromolyn with doses of 25 and 50 mg/kg/day significantly increased PTZ-induced number of spike waves in comparison to the control group in freely moving pups (P<0.01). However, there was not a difference between 25 and 50 mg/kg/day of cromolyn groups (P>0.05). In addition, cromolyn with doses of 25 and 50 mg/kg/day significantly increased PTZ- induced amplitude of spike waves in comparison to the control group in freely moving pups (P<0.01). However, there was no significant difference between 25 and 50 mg/kg/day of cromolyn groups (P>0.05). The spike amplitudes were 1069±276; 2068±639 and 2319±496 µV, respectively.

The time interval between PTZ injections to the appearance of the first electrographic seizure are presented in Fig.3. Cromolyn treatment groups (cromolyn 25 mg/kg/day and 50 mg/kg/day) dose-dependently decreased onset of seizure in comparison to the control group (P<0.05). However, there was no significant difference between 25 and 50 mg/kg/day of cromolyn groups (P>0.05). The mean latencies to first EEG

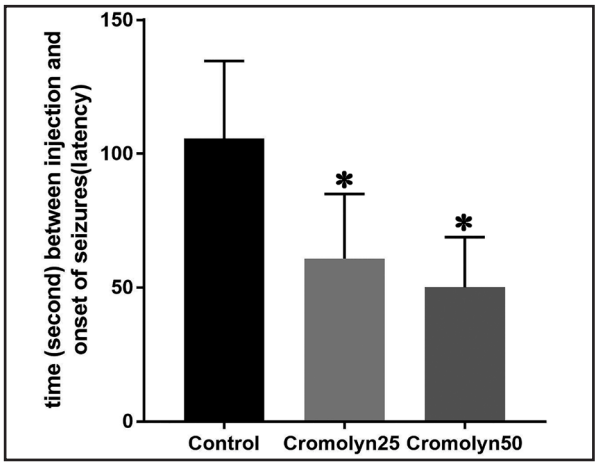

Figure 3. Time (second) between injection to onset of seizures in pups after prenatal Cromolyn exposure in 25 mg/kg/day (n=8) and 50 mg/kg/day (n=8) is significantly decreased compared to control (n=8). *P<0.05.

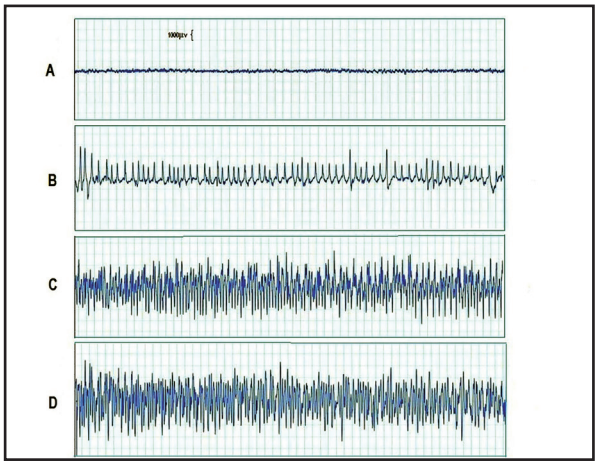

Figure 4. Spike-wave morphology during seizure episode in different groups is shown. A, Baseline. B, Control Group. C, 25 mg/kg cromolyn. and D, 50 mg/kg cromolyn.

seizure event in seconds following PTZ injections in different groups were: control group: 105.27 ± 44; cromolyn 25 mg/kg/day: 60.85 ± 39 and cromolyn 50 mg/kg/day: 50 ± 31. In addition, the spike wave morphology during seizure episode in different groups is shown in Fig. 4.

Discussion

We evaluated the effects of cromolyn in electrographic and behavioral aspects. Our findings suggest that gestational exposure of cromolyn can enhance epileptiform activities in offspring. Decreasing seizure time latency and increasing frequency/amplitude of the spikes in treatment groups clarifies the epileptogenic effect of cromolyn. In addition to electrographic measurements, parallel behavioral observations could be a confident proof for this claim. Both applied doses of cromolyn (25 and 50 mg/kg) have shown significant difference in comparison to the control group.

Comparing the epileptogenicity of 25 and 50mg/kg doses, there were some differences in electrographic aspect, but they were not statistically significant. This is while there were almost no differences in behavioral aspect. So it appears that when seizure behavior reaches the maximal level, it can no longer be affected by increasing brain electrical activity. No evident change in seizure susceptibility by doubling the cromolyn dosage is a matter of controversy. For explaining this event, it can be assumed that 25mg/kg cromolyn provides sufficient mast cell stabilization so that the higher dose cannot impose further impact

Cromolyn has been long known as an anti-inflammatory agent acting through stabilizing mast cell membrane and preventing mediator release. Histamine is the most important mediator in mast cells (Krystel-Whittemore, et al. 2015) and is known to be involved in seizure occurrence (Kukko-Lukjanov, Lintunen et al. 2010). Regarding the protective role of histamine in seizure susceptibility any disturbance in its secretion could lead to more seizure incidence (Benarroch, 2010). As mentioned earlier some studies have shown the epileptogenic effects of mast cell stabilizers (Yamada, et al. 2012; Yokoyama, et al. 2012). Inversely, Valle-Dorado et al. (2016)

reported antiepileptic effects of mast cell stabilizers in lithium-pilocarpine model of temporal lobe epilepsy (Valle-Dorado, et al. 2016). Nevertheless, it is unclear whether any of these effects could apply to gestational period and influence future offspring. Although the critical role of histaminergic system during developmental stages is implied (Molina-Hernandez, Diaz et al. 2012), still no research has been conducted to evaluate the effect of mast cell stabilizers during embryogenesis. This issue becomes even more important when it comes to knowing that cromolyn "as the most important mast cell stabilizer" is introduced to be safe during pregnancy (Laurence et al. 2005). Of course, it should not to be missed that the absorption of cromolyn from gastrointestinal tract is low when taken orally, but it is believed that it could be more absorbed through inhalation applications (Yoshimi, et al. 1992) which is the most popular form in chronic asthma (van der Wouden, et al. 2008).

Putting our findings altogether suggests reconsideration in cromolyn application during gestational period especially in families with seizure background, although further studies for more definite evidences may be required. For instance, other routes of cromolyn administration (considering contradictions about the agent's absorption) or other mast cell stabilizing agents be considered. Also, according to previous studies the brain of 14-day-old rats is equivalent to the brain of human infants with one year of age (Gholipoor, Saboory et al. 2013), so regarding the plasticity of mast cells population during different developmental stages (Khalil, Ronda et al. 2007), targeting other time intervals would not be pointless at all.

Conclusion: Our study for the first time reveals enhanced epileptiform activity in developing rats due to prenatal exposure of sodium cromoglycate.

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اثر مواجهه جنینی با سدیم کروموگلیکات روی فعالیت‌های شبه صرعی در نوزاد موش صحرایی

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چکیده

زمینه مطالعه: امروزه صرع یکی از شایع‌ترین اختلالات عصبی جهان است. مست سل‌ها منبع اصلی هیستامین مغزی بوده و هیستامین موجود در آن‌ها نقش مهمی را در تعدیل تشنج ایفا می‌کند. سدیم کروموگلیکات جزء داروهای تثبیت کننده مست سل‌ها و به عنوان خط اول درمان در بیماری‌های آسم و ماستوسیتوز پیشنهاد شده است.

هدف: هدف از این مطالعه ارزیابی اثر قرار گرفتن در معرض سدیم کروموگلیکات در دوره حساس بارداری بر استعداد بروز تشنج در فرزندان است.

روش کار: در این مطالعه ۱۲ سر موش صحرایی ماده به طور تصادفی به ۳ گروه تقسیم شدند (n=۴) که شامل: دو گروه پیش درمانی که دوزهای مختلف ۲۵ mg/kg و ۵۰ سدیم کروموگلیکات را بصورت داخل صفاقی و در طول هفته آخر آبستنی دریافت کردند و گروه شاهد که با حجم برابر (۰/۵ ml) بافر فسفات سالین دریافت کرد. در روز ۱۲ پس از زایمان، ۸ نوزاد از میان فرزندان هر گروه انتخاب شدند. نوزادان پس از بیهوشی به دستگاه استریوتاکسی منتقل شده و میکرو الکترودها از طریق جراحی بر روی قشر مغز قرار گرفتند. پس از ریکاوری نوزادان، فعالیت‌های شبه صرعی ناشی از پنتیلن تترازول بررسی شد.

نتایج: داده‌های الکتروگرافیک گروه سدیم کروموگلیکات نشان دهنده کاهش در زمان تأخیر تشنج (زمان تزریق تا بروز اولین فعالیت تشنجی) و افزایش فرکانس/دامنه اسپایک‌های تشنجی در مقایسه با گروه شاهد بود ($p<۰/۰۵$). همچنین بررسی فایل‌های ویدیویی نشان دهنده همسو بودن داده‌های رفتاری با وقایع الکتروگرافیک بود.

نتیجه‌گیری نهایی: نتایج به دست آمده حاکی از افزایش استعداد بروز تشنج در نوزادانی است که در دوره جنینی با سدیم کروموگلیکات مواجهه داشته اند.

واژه‌های کلیدی: فعالیت شبه صرعی، مواجهه جنینی، نوزاد، موش صحرایی، سدیم کروموگلیکات

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