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"Incremento de la impulsividad tras activación inmune temprana y tratamiento con antibiótico: estudio en un modelo animal"

"Impulsivity increase after perinatal immunoactivation and antibiotic treatment: study in animal model"

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INDEX

ABSTRACT

Immune activation during early developmental stages has been proposed as a contributing factor in the pathogenesis of neuropsychiatric disorders like obsessive-compulsive disorder (OCD), Tourette's and ADHD, while antibiotic post-treatment seem to act as a preventor. However, the relationship between these factors and the vulnerability to inhibitory control deficit (found in several neuropsychiatric conditions such as schizophrenia and OCD) is not known yet. This work studied if an animal model of human early life infection -postnatal immune activation- could lead to an increased vulnerability to impulsive and/or compulsive behaviours during adulthood in rats, and the modulatory role that antibiotic may have. A cohort of forty-eight male Wistar rats was exposed to Group A streptococcus (GAS) antigen at PND35 (with two boosts two and four weeks later). During GAS exposure, half of the animals were treated with broad-spectrum antibiotic Ampicillin (1 mg/ml). In the adult period (>PND90), inhibitory control was assessed by the selective attentional 5-choice serial reaction time task (5-CSRTT) and the Delay discounting task (DDT). On this experiment, GAS seemed to lead rats to show more impulsive responses on 5-CSRTT, while ampicillin seemed to prevent impulsive choice in the 20" phase of DDT when comparing the two GAS-treated groups, although it had no effect on the rest of phases and on 5-CSRTT. This data shows a possible relationship between immune activation during critical periods and inhibitory control impairment in adult period, revealing the modulatory effect of antibiotic ampicillin.

Keywords: perinatal immunoactivation, Group A Streptococcus, antibiotic, inhibitory control, impulsitivity, compulsivity, 5-CSRTT, DDT.

RESUMEN

La inmunoactivación en etapas del desarrollo tempranas se ha propuesto como un factor que contribuye en la patogénesis de desórdenes neuropsiquiátricos como el Trastorno Obsesivo-Compulsivo (TOC), Síndrome de Tourette o Trastorno por déficit de Atención e Hiperactividad, mientras que el antibiótico post tratamiento parece actuar como protector. Sin embargo, la relación entre estos factores y la vulnerabilidad a los déficits en control inhibitorio (encontrados en varios trastornos neuropsiquiátricos como esquizofrenia o TOC) no es del todo conocida. En este trabajo se investiga si un modelo animal con una infección en una etapa temprana -inmunoactivación postnatal- podría dar lugar a un aumento en la vulnerabilidad a comportamientos impulsivos o compulsivos en ratas durante la adultez y el rol modulatorio que el antibiótico podría tener. Una muestra de 48 ratas Wistar macho fue expuesta a antígeno del Estreptococo del grupo A (GAS) en día postnatal 35 (PND35) (con dos recuerdos o boosts del antígeno dos y cuatro semanas después). Durante la exposición a GAS, la mitad de los animales fue tratado con un antibiótico de amplio espectro llamado Ampicilina (1 mg/ml). En la adultez (>PND90), fue evaluado su control inhibitorio mediante la tarea de atención selectiva 5-Choice Serial Reaction Time Task (5-CSRTT) y la tarea sobre toma de decisiones impulsiva Delay Discounting Task (DDT). En el experimento, el tratamiento con GAS dio lugar a ratas que mostraron mayor número de respuestas impulsivas en 5-CSRTT, mientras que la Ampicilina previno las elecciones impulsivas en la fase 20” de DDT cuando comparamos los dos grupos tratados con GAS, aunque no tuvo efecto en el resto de fases de esta tarea ni tampoco de 5-CSRTT. Estos datos nos muestran una posible relación entre la inmunoactivación en período de desarrollo y los déficits en control inhibitorio en la etapa adulta, desvelando el efecto modulador del antibiótico ampicilina en la expresión de la conducta.

Palabras Clave: inmunoactivación temprana, GAS, estreptococo, antibiótico, control inhibitorio, impulsividad, compulsividad, 5-CSRTT, DDT.

1. INTRODUCTION

Inhibitory control could be defined as a cognitive and behavioral process to inhibit responses, memories, thoughts, perceptions or postpone gratifications (Bari & Robbins, 2013). Several authors consider that inhibition is one of the main and unifying components of executive control (e.g., Barkley, 1997; Zacks et. al., 1994; Dempster and Corkill, 1999). Thus, failures in inhibitory control lead to impulsive and/or compulsive behaviors. (Robbins and cols., 2011).

Within the inhibitory control deficit spectrum, impulsivity is generally considered a consequence of disabled executive functioning. More concretely, the co-occurrence of dysfunctional inhibitory processes and strong impulses determines the impulsive action, which also is triggered and modulated by dispositional and situational variables (Hofmann et al., 2009; Metcalfe and Mischel, 1999). Impulsivity could be defined as the disability to inhibit a prepotent response (Moreno et al, 2010). On the other side, compulsivity is define as inappropriate persistent actions according to the situation, without relationship to the general goal, that frequently result in undesirable consequences. Both constructs have been hypothesized to result from response inhibition failures or ‘‘topdown’’ cognitive control malfunctions. (Robbins and cols., 2011).

Many psychiatric affections are characterized by the presence of impulsive and compulsive traits (Bari & Robbins, 2013), such as attention deficit/hyperactivity disorder (ADHD) (Nigg, 2001), drug addiction (Jentsch and Taylor, 1999), schizophrenia (Gut-Fayand et al., 2001), compulsive eating and obesity, compulsive gambling, obsessive-compulsive disorder, anxiety or depression (Fernando & Robbins, 2011).

Currently, several researches are trying to establish the causes of these problems. One of these proposed factors is the perinatal immunoactivation (Benros et al., 2014) which affirm that immunoactivation in sensitive period could produce vulnerability to several neuropsychopatology disorders. As example of this, we find PANDAS (Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococci) (Snider & Swedo, 2003). These disorders encompassed by the name of PANDAS are originated by exposure to Group A Streptoccocus (GAS), the pharyngitis tonsillitis bacteria and it seems lead to all neuropsychiatric disorders above-named (Lotan et. al, 2014). It has been proposed that GAS infection induces the production of antibodies against GAS and neuronal determinants, through the process of molecular mimicry (Bonthius & Karacay, 2003; Cunningham, 2012). This autoimmune response can also target the central nervous system, leading to neurological and psychiatric disorders, such as Sydenham’s chorea (SC), obsessive-compulsive disorder (OCD), and Tourette’s syndrome, and as we said before PANDAS (Dale, 2005).

Thus, it emerges a preclinical animal model of streptococcal-related neuropsychiatric disorders. In this model, after GAS exposure, rats exhibited impaired food manipulation (Brimberg et al, 2012; Lotan et al, 2014), increased marble-burying without a concomitant increase in activity level (Lotan et al, 2014), impaired fine motor control (Gordon, 2009; Swedo et al, 1993; Demiroren et al, 2007), anxiety (Demiroren, et al, 2007; Dale, et al, 2004; Ridel, et al, 2010; Swedo, et al, 1998), compulsions (Swedo, et al, 1994; Dale et al, 2004; Swedo, et al 1998; Asbahr, et al 2007) and increased induced-grooming (Gordon, 2009; Murphy et al, 2007; Swedo et al, 1989). As we can see, most of symptoms of this syndromes are in the impulsivity-compulsivity continuum.

On the other hand, there are many researchers that suggests that continued antibiotic treatment throughout childhood may prevent or attenuate these GAS-related neuropsychiatric disorders (Bonthius & Karacay. 2003; Gordon, 2009; Snider, et al, 2005). For instance, Lotan et al. (2014) found that Ampicillin treatment eliminated the impairment in food manipulation, and tended to attenuate the increased marble burying in GAS-exposed rats (Lotan et al, 2014).

Impulsivity and compulsivity symptoms were assessed with the aim of the Five Choice Serial Reaction Time Task (5-CSRTT). This task requires animals to detect brief flashes of light presented pseudorandomly in one of five holes and to make a nose-poke response in the correct spatial location in order to receive a food reward (Moreno, et al., 2010, 2012). Generally, the accuracy of stimulus discrimination provides an index of attentional capacity, while premature responses—made before the presentation of the stimulus—are regarded as a form of impulsive behavior and hence a failure in impulse control. Additional responses in any of the five holes or in the food magazine are recorded as perseverative, which is often interpreted as a form of compulsive behavior (Robbins, 2002). In order to asses another types of impulsivity, we used Delay Discounting Task. This task measure the impulsive choice through responses in one of two levers associated to different pellet-rewards (Moreno, et al. 2010).

2. MATERIALS AND METHOD

2.1. Animals

The animals arrived at the lab weighing 250-300 g, and were housed four rats/cage (50×35×20 cm) at 22°C, with a 12:12-h light–dark cycle (lights off at 07:00 h), environmental enrichment and food and water provided ad libitum. Before behavioural testing, rats were gradually reduced to 85% of their free-feeding body weight through controlled feeding, and their body weights were maintained at this level of deprivation throughout the experiment. Food was provided by daily feedings of lab chow approximately 30 min after each experimental session. All testing was

performed between 09:00 and 14:00 h. All procedures were performed according to the Spanish Royal Decree 53/2013 on the protection of experimental animals and the European Community Council Directives (86/609/EEC).

2.2. Experimental design

Subjects were assigned to four different experimental conditions. Depending on treatment and post-treatment, the resulting four groups were: saline-water (SAL-H_2O), saline-antibiotic (SAL-AMP), GAS-water (GAS-H_2O) and GAS-antibiotic (GAS-AMP). The number of animals on each group was n=12. Once animals reached PND90, food-deprivation began and behavioural assessment started.

2.3. Group A streptococcus (GAS) exposure

Antigen for *Streptococcus pyogenes*, protein type 1 (CECT, Paterna, Spain) was administered following Brimberg et al. (2012) and Lotan, et al. (2014).

Briefly: After initial habituation and before exposition, animals were handled daily. The first exposure was at PND35. GAS group was immunized subcutaneously with 200 μl of 1:1 emulsion of PBS containing 1.2 mg of the GAS antigen and Complete Freund´s adjuvant (CFA, Sigma-Aldrich, Madrid, Spain) supplemented with 4 mg/ml of heat-killed mycobacteria H37RA (BD, San Agustin de Guadalix, Spain). Two boosts were introduced two and four weeks after the first exposure, where each rat was boosted with 200 μl 1:1 emulsion of incomplete Freund´s adjuvant (IFA, Sigma-Aldrich, Madrid, Spain) in PBS containing 1.2 of GAS antigen. With the purpose of increasing the permeability of the blood brain barrier (Linthicum, et al., 1982), rats received an intraperitoneal injection of 10^{10} heat-killed *Bordetella pertussis* (BD, San Agustín de Guadalix, Spain) as an additional adjuvant.

Control animals were injected with PBS and adjuvants only.

2.4. Antibiotic treatment

Broad spectrum antibiotic Ampicillin (Reig Jofré, Sant Joan Despí, Spain) was used as post-treatment following Lotan et al. (2014). SAL-AMP and GAS-AMP groups were administered with drinking water supplemented with Ampicillin in their home cages in a dose of 1 mg/kg, from the first day of GAS treatment until one week after the last boost.

SAL-H_2O and GAS-H_2O groups were given regular drinking water.

2.5. Illness assessment

A short version of the *Functional Observational Battery* (FOB) (Moser, 1995; Sánchez-Santed, 2004) was used 2 and 24 hours after GAS treatment so as to assess illness symptoms. Parameters were: piloerection, diarrhea, tremor, salivation, lacrimation and flat or hunched posture, plus weight and temperature.

2.6. 5-Choice serial reaction time task (5-CSRTT)

Rats were tested in twelve operant SIP chambers (32×25×34 cm) (MED Associates, St. Albans, VT). A detailed description of the apparatus has been previously provided (Moreno et al. 2010). The scheduling and recording of the experimental events was controlled using a computer and commercial software Med PC (Cibertec SA, Spain).

Animals were required to respond to brief flashes of light presented randomly in one of five spatial locations (Carli et al. 1983). Pre-training and training were based on previous procedures with subtle modifications (Bari et al. 2008; Robbins 2002). A detailed description of the apparatus and procedure has been provided previously (Moreno et al. 2010; Moreno et al., 2012). The animals were rated on the 5-CSRT task with a specific performance criterion (correct responses >50, accuracy >80%, omissions <20%), with an SD of 1 s. Each daily session consisted of 100 discrete trials with stable performance being achieved after about 40 sessions. Each test session commenced with the illumination of the chamber by the house light and of the food magazine in which a food pellet was delivered. The collection of this pellet from the feeder started the first trial, and the next trials were self-initiated by a nose poke response in the food magazine; then, the light of the food magazine was extinguished and a fixed inter-trial interval (ITI) of 5 s started. At the end of the ITI, a visual stimulus of 1-s duration (SD) was presented in a random location of the apertures at the rear. Responses in this aperture within 5 s, the limited hold (LH), were recorded as correct responses and were rewarded by a food pellet delivery in the magazine feeder with its illumination. Response errors were omissions (failure to respond to the stimulus within the LH), errors of commission (responses made to the wrong location), and premature responses (responses made before the presentation of the visual stimulus in any of the five apertures during ITI). The consequence for any of these response errors was a 5-s period of darkness (time-out), during which no food was delivered. An additional response in an aperture after a correct response and before the food collection was recorded as a perseverative response and had no consequence of a time-out period; the collection of the pellet from the feeder started in the next trial. A response in the food magazine after the delivery of food or after a timeout period initiated the next trial; a response in the food magazine after a premature response restarted the same trial. Each session terminated after 100 trials or after 30 min. To facilitate acquisition of the 5-CSRT task, the SD of the target stimuli was progressively shortened from 8 to 1 s. Thus, in stage 1, SD=8 s with LH=10 s and ITI=5 s, while the SDs of stages 2 to 5 were 6, 2.5, 1.25 and 1 s, respectively (LH and ITI=5 s). Animals advanced through stages by completing at least 50 correct trials with >80% accuracy and <20% omissions. The measures recorded were as follows: accuracy (percentage of correct trials=correct trials/correct trials + incorrect trials×100), n° correct responses, n° incorrect responses, percentage of omission (number of omissions/correct responses+incorrect responses+omissions×100), n° premature responses, n° perseverative responses and latencies (in

seconds) to correct response from stimulus presentation to a correct nose poke and to the reward of a food pellet in the magazine after a correct response.

2.7. Delay Discounting Task

In this task, response on one lever (A) produced a one-pellet reward; response on the other lever (B) produced a four-pellet reward. Each session consisted of 60 trials, 30 forced choice and 30 free choice in which both levers were presented. Illumination of the house light and tray light signaled the start of each trial. A nose-poke response was required in the food pellet receptacle to initiate lever presentation. Failure to make the response or to depress the lever within 10 s terminated the trial. When either lever was pressed, the house light turned off, the 'clicker' sounded, and both levers were retracted. Food reward was then delivered, either almost immediately or after a delay. The experiment was divided into five sets of five sessions. During the first set, both levers had a delay of 0 s. The delay to reward A remained constant at 0 s throughout the experiment, whereas the delay to reward B increased to 10 s in set 2, 20 s in set 3, and 40 s in set 4. Set 5 was identical to set 1: levers A and B were both 0 s (Moreno, et al, 2010).

Figure 1. Timeline of experiment. Two boosts were introduced 2 and 4 weeks after the first immune activation*.

2.8. Statistical Analyses

Analyses of variance (ANOVAs) were carried out for FOB, 5-CSRTT and DDT. For FOB a two way ANOVA (Vs: treatment and antibiotic) was performed. For 5-CSRTT and DDT repeated measures ANOVA (RM: phases; Vs: treatment and antibiotic) was performed.

3. HYPOTHESIS AND OBJECTIVES

Following to all the information exposed before, we could think that GAS exposure during a sensitive period could produce vulnerability to several neuropsychiatric disorders, thus leading to an inhibitory control impairment.

Therefore, the present study has as the main objective to unveil how perinatal immunoactivation affects to inhibitory control and if antibiotic treatment might prevent or attenuate impulsivity and compulsivity symptoms.

For this reason, the main objectives were:

- To study the long-term effects on inhibitory control paradigms in the adult period of perinatal immunoactivation, through the exposure to Group A Streptococcus (GAS) antigen.
- To study if the antibiotic treatment, counteracts the long-term effects on inhibitory control paradigms in the adult period of perinatal immunoactivation, through the exposure to Group A Streptococcus (GAS) antigen.

The porposed hypothesis were:

- GAS will induce a decreased inhibitory control showed by increased impulsivity in the 5-CSRTT and increased impulsive choice in Delay Discounting task in the adult period, compared vehicle exposure.
- The co-administration of antibiotic treatment with GAS could have protective effect, and these group will not develop an increased inhibitory control deficit.

4. RESULTS

This preclinical animal model of streptococcal-related neuropsychiatric disorders has been shown as a potent model and it has been used in other researches as Lotan, et al, 2014.

4.1. Functional Observational Battery (FOB)

The results of FOB are shown in figure 2. After GAS exposure, GAS-H2O and GAS-ANT, differed in terms of weight from their vehicle-treated counterparts (interaction day x treatment: $F_{1, 44}$= 5.1563, p<0.0001). There are not significant differences between GAS groups and Vehicle in temperature (treatment, $F_{1, 44}$=0.13, p=0.71; antibiotic, $F_{1, 44}$=1.81, p=0.18). Concerning piloerection there was no observable effects in any of the groups, to such an extent that at two hours there was no variance so ANOVA could not be performed.

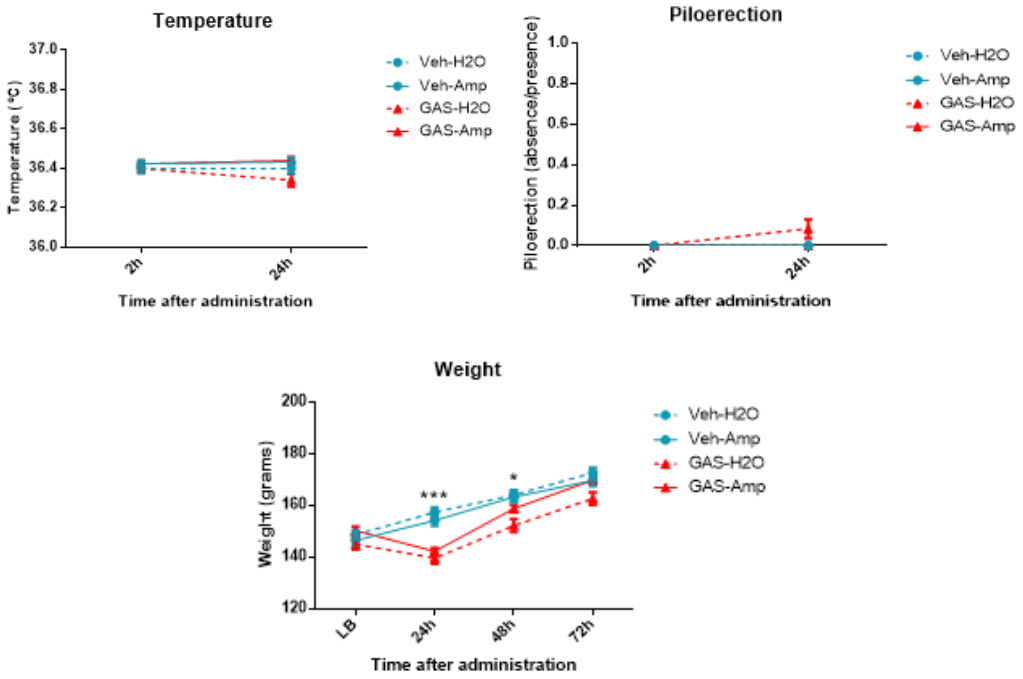

Fig. 2. Results of FOB. Measures of weight, temperature and piloerection after GAS exposure and Ampicillin treatment.

4.2. 5-Choice Serial Reaction Time Task

4.2.1. Acquisition

The results of acquisition in 5-CSRTT are shown in figure 3. There are not significant differences between groups in the acquisition of the task (Treatment x Antibiotic, $F_{1, 44}$=0.99, p=0.32; Treatment, $F_{1, 44}$=0.19, p=0.66; Antibiotic, $F_{1, 44}$=0.23, p=0.62; Phase, $F_{4, 176}$=89.82, p=0.0000).

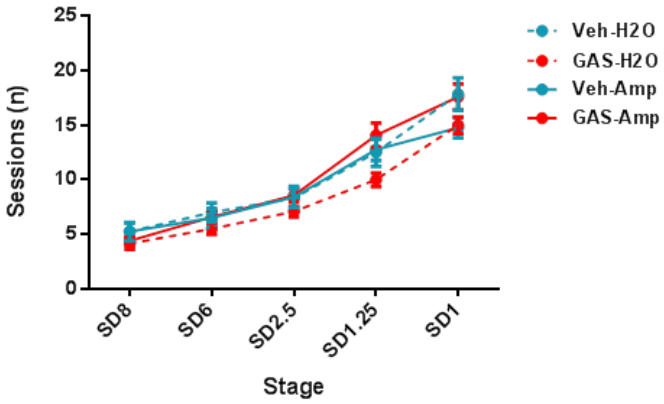

Figure 3. The mean of results in acquisition across 20 sessions of 5-CSRTT. There was not significant differences between groups.

4.2.2. 5-Choice Serial Reaction Time Task (Base line)

Statistical analyses indicate significant differences in premature responses (Treatment x Antibiotic, $F_{1, 44}$=1.5313, p=0.22247; Treatment, $F_{1, 44}$=4.1121, p<0.05; Antibiotic, $F_{1, 44}$=2.2158, p=0.14374). There are not significant differences in omissions (Treatment x Antibiotic, $F_{1, 44}$=2.05, p=0.15), accuracy (Treatment x Antibiotic, $F_{1, 44}$=0.35, p=0.55) and perseverative responses (Treatment x Antibiotic, $F_{1, 44}$=2.99, p=0.09).

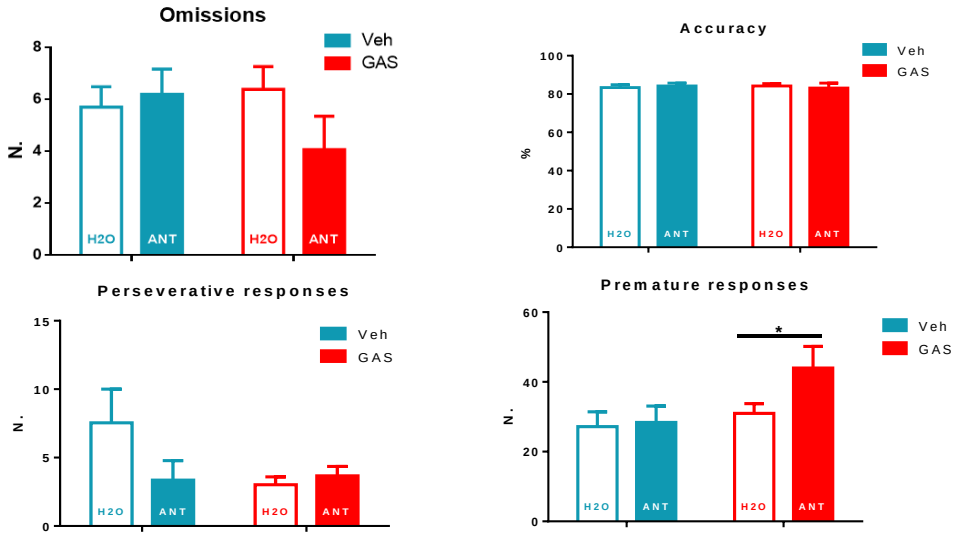

Figure 4. The mean of omissions, accuracy, perseverative responses and premature responses in 5-CSRTT. Statistical analyses indicate significant differences in premature responses between Veh-H2O and GAS-H20 regarding to GAS-ANT.

4.2.3. Delay Discounting Task (DDT)

The results of DDT are shown in figure 5. There were no significant differences between groups in DDT neither in Treatment nor in antibiotic exposure (Treatment x Antibiotic, $F_{1, 44}$=0.11, p=0.73). However when comparing only GAS-treated animals differences were observed at delay=20" ($F_{4, 88}$ = 3.84; p<0.01; GAS-H2O vs. GAS-ANT at delay=20": p< 0.001).

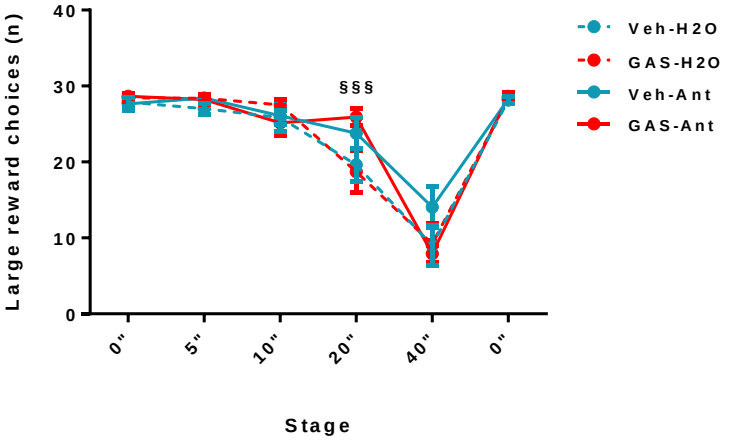

Figure 5. The mean choices of delayed reward between groups. § symbol means differences between GAS-H2O and GAS-ANT groups.

5. DISCUSSION

The present study investigated the streptococcal model in inhibitory control and the potential therapeutic role of antibiotic treatment to attenuate impulsive and compulsive symptoms. The findings showed that GAS affected to weight gain in first 24 hours after exposure, although both GAS groups reached the same weight than Vehicle groups after 72 hours, according to FOB. Moreover, results show that GAS and Ampicillin administration lead to more premature responses in 5-CSRTT, while no differences existed in task performance, learning and memory, or perseverative responses. Finally, no differences existed concerning treatment in DDT but at delay=20" there was an effect of antibiotic treatment.

Exposure to GAS antigen provoked significant differences in weight gain in GAS groups, during the first 48 hours after exposure. GAS-treated animals had a strong decrease in body weight 24 and 48 hours when compared to their vehicle-treated counterparts, reaching them only after 72 hours. Weight loss and poor appetite are solid indicators of sickness (Kelley, et al. 2003; Dantzer and Kelley, 1989). However no effect on temperature and piloerection were found.

In 5-CSRTT GAS exposure had an effect on premature responses where GAS-treated animals showed impulsive-like behavior than Vehicle-treated. However neither GAS exposure nor antibiotic treatment had any effect on perseverative (that is, compulsive) responses on this task. No effect was found on acquisition or any of the remaining baseline variables. This results in inhibitory control are in concordance with results of Lotan, et al. 2014b using the same protocol, although their findings showed compulsive behavior and our findings showed impulsive behavior. There is previous evidence (Yaddanapudi, et al., 2010) of an increased number of premature responses in a reversal spatial learning. There is also wide evidence about inhibitory control impairment after GAS exposure in terms of stereotyped responses (Brimberg, et al. 2012; Zhang, et al. 2012; Lotan, et al., 2014b). This dissociation between impulsive and compulsive behavior does not contradict the literature because in neuropsychiatric disorders that exhibit inhibitory control impairment could exist both or only some of them (Robbins, et al. 2012).

In DDT, although no overall differences were found on either variable, when comparing the two GAS-exposed groups, antibiotic effect is found at delay=20", where ampicillin-treated animals were more prone to choose the large reward. This can be seen as a protective effect induced by antibiotic treatment, given that these animals are more resistant to reinforcement delay and still prefer the large reward. This is in concordance with the protective effects reported by Lotan et al. (2014a), where ampicillin prevented animals to exhibit inhibitory control problems, but in conflict with the 5-CSRTT results, where it did not protect GAS-exposed rats from impulsive behaviours. Antibiotic treatment, thus, might have a complex role concerning inhibitory control deficit.

Our study suggest that GAS can create a vulnerability to inhibitory control deficit, but several factors might underlie this kind of conditions. Research suggest that reported symptoms result from a combination of local, regional, and systemic abnormalities (Hamilton, et al., 2001; Benoist, et al., 2001; Snider, et al., 2003; Levin, et al., 2002). Magnetic resonance imaging scans have revealed enlargements of the caudate, putamen and globus pallidus, which points to regional inflammatory changes (Perlmutter, et al., 1999; Swedo, et al., 1999) and the presence of serum antibodies wich cross-react with neurons of the caudate, putamen, and globus pallidus, lead to local autoinmune reactions (Kiessling, et al., 1994; Giedd, et al., 1996). In the same way and according to findings of Brimberg et al. (2012), the type of antibodies deposited in the structures previously cited and also in thalamus and frontal cortex, is Immunoglobulin G (IgG) that has an important role in the pathogenesis of impulsive and compulsive symptoms typical of PANDAS.

6. CONCLUSIONS

In this study we investigated the effects of GAS antigen on inhibitory control and the potential therapeutic role of antibiotic as a preventor of impulsive and/or compulsive symptoms. We have found that GAS exposure produced a significant weight decrease which is a firm indicator of sickness. Moreover, we found that GAS and ampicillin affected inhibitory control leading to more premature responses. Concerning DDT, our findings showed that antibiotic treatment could have a protective effect because treated animals were more prone to take the large reward. Future studies should elucidate the role of these factors in the development and/or ressistance to neuropsychiatric disorders, in order to have a better understanding and, ideally, to develop preventive and treatment protocols.

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