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Latent inhibition threshold in *Roman high-avoidance* rats: a psychogenetic model of abnormalities in attentional filter?

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Introduction. Basic research devoted to the study of the psychobiological anomalies of schizophrenia, as well as of its treatments, has used animal models in which some psychotic-like symptoms are induced by administration of psychostimulant drugs. There is, however, a growing necessity of having animal models presenting better construct validity, i.e., animal lines spontaneously showing phenotypes associated to the psychotic spectrum (for instance, enhanced sensitivity to psychostimulants, or cognitive and attentional anomalies characteristic of schizophrenic disorders). Several lines of evidence suggest that the RHA *(Roman high-avoidance)* rat strain presents a neurobehavioral profile which is consistent with such goals.

Methods. RHA rats were compared to Sprague-Dawley (SD) rats (as a standard control strain) for the expression of latent inhibition (in a 100-trial session of two-way active avoidance) under threshold conditions (i.e., only 15 preexposures to the conditioned stimulus were administered).

Results. Under such experimental conditions SD rats showed significant latent inhibition of the two-way active avoidance response (both during the first 50 trials and in the whole 100-trial session), while that attentional phenomenon did not appear in the RHA strain.

Conclusions. The experimental results obtained here indicate that RHA rats display a deficit of latent inhibition at threshold conditions, an information processing (or attentional) anomaly which typically appears in schizophrenic patients. It is proposed that RHA rats might be an useful animal model for the study of vulnerability to some schizophrenic symptoms. This conclusion is supported by data that indicate that latent inhibition deficits are a characteristic attentional abnormality of these diseases.

Key words:
Schizophrenia. Animal models. RHA rats. Latent inhibition. Attentional deficits.

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El umbral de inhibición latente en las ratas *romanas de alta evitación:* ¿un modelo psicogenético de anomalías en el filtraje atencional?

Introducción. Además de los modelos animales basados en la inducción de síntomas «psicóticos» mediante fármacos psicoestimulantes, en la investigación sobre las alteraciones psicobiológicas de la esquizofrenia y sus tratamientos es cada vez más patente la necesidad de modelos que posean mayor validez de constructo, tales como líneas de animales que presenten espontáneamente singularidades asociadas a los trastornos psicóticos (p. ej., una mayor sensibilidad a los efectos de los psicoestimulantes o las anomalías cognitivas/atencionales típicas de los síndromes esquizofrénicos). Diversas evidencias experimentales indican que la cepa de ratas RHA *(romanas de alta evitación»)* muestra un perfil neurobiológico y conductual consistente con tales requisitos.

Métodos. Utilizando ratas RHA, en comparación con ratas Sprague-Dawley (SD) como un control estándar, se evaluó la expresión de inhibición latente (en una sesión de 100 ensayos de evitación activa en dos sentidos) en ambas cepas y en condiciones de umbral (con sólo 15 preexposiciones al estímulo condicionado).

Resultados. Las ratas SD muestran en tales condiciones inhibición latente significativa en los 50 primeros ensayos y en el total de la sesión, fenómeno atencional que no aparece en la cepa RHA.

Conclusiones. El déficit en inhibición latente en condiciones umbral, que mostraron los animales RHA, es compatible con la idea de que dicha cepa puede representar un modelo útil para el estudio de la vulnerabilidad a las alteraciones del espectro esquizofrénico. Una conclusión avalada por los datos que indican que los déficit en inhibición latente son una anomalía atencional característica de aquellas patologías.

Palabras clave:
Esquizofrenia. Modelos animales. Ratas RHA. Inhibición latente. Déficit atencionales.

INTRODUCTION

Research on psychobiological abnormalities involved in schizophrenia needs laboratory animal models having construct validity, that is, that imitate both symptom aspects and neural processes involved in the disorder besides having predictive validity regarding treatment effects. Psychostimulant drugs are generally administered in order to induce «schizophrenic states» in animals, a strategy that stresses the role of dopaminergic neurotransmission in the symptoms induced while keeping certain predictive validity. One possible alternative, that offers the advantage of greater construct validity (and heuristic potential) is that of finding rodent strains vulnerable to this «schizophrenic state» and studying in them the alterations present in psychological and neurobiological conditions as well as treatment effects[1,2].

Some advances have already been produced in this sense. This is reflected, for example, by the Ellenbroek et al.[2] study that shows that rat strain APO-SUS, pharmacogenetically selected by its extreme sensitivity to the effects of apomorphine, has attentional deficits in comparison with the APO-UNSUS strain. These deficits have been shown in paradigms of latent inhibition and prepulse inhibition of the startle response, which have also been studied and corroborated in schizophrenic patients[3,4,5]. Several neurobiological characteristics of the APO-SUS rats strengthen the construct validity of this strain as genetic model of at least certain aspects of schizophrenia[2].

In the present study, we present the results obtained in another line of rats that has been studied in recent years in relationship with its possible validity as a model of characteristic attributes of schizophrenia. The *Roman high-avoidance* (RHA/Verh) and *Roman low-avoidance* (RLA/Verh) rat strains are derived from the psychogenic selection (bidirectional) due to their facility (RHA/Verh) or incapacity (RLA/Verh) to acquire two-way active avoidance response in the shuttlebox[6,7,8]. The RHA/Verh performat about 70% (or more) avoidances in typical sessions of 50 trials, while the RLA/Verh do not generally exceed 5% of avoidance responses, due to greater emotional/anxiety reactivity and tendency to freeze (due to conditioned fear) of the latter[7,9,10]. Both strains also have multiple differences in their response profiles, both on behavioral as well as neuroendocrine/neurochemical measures, in many experimental situations. Besides showing less emotional reactivity (behavioral and neuroendocrine) to stress[7,8,11,12] and less anxiety and conditioned fear[13], RHA/Verh rats have (regarding RLA/Verh strain) less learning capacity and working memory in different tests[11,14], greater impulsivity and incapacity to inhibit irrelevant responses (in situations in which such responses interfere with learning[15,16]), greater preference to novelty seeking and to gratifying substances and drug abuse[17-20], greater mesocortical dopaminergic response to stress[21,22], greater mesolimbic dopaminergic response to abuse drugs (cocaine, morphine, alcohol) and greater locomotor sensitization to repeated administration of psychostimulants and opiates[23-25]. See a summary of the principals characteristics of RHA and RLA rats in table 1[26-30].

The relative deficit of the RHA rats in working memory and learning paradigms and in conditioning tests (e.g., classic conditioning of fear; fear potentiated startle response[10,13]), alongside their incapacity to inhibit irrelevant responses (impulsivity) in different tasks[15,16], their prefrontal dopaminergic hyperactivation in response to stress[21,22] and their mesolimbic dopaminergic hyperactivation (and greater locomotor sensitization) after administration of psychostimulants[23,24] (table1), all suggest that this rat strain may have attentional abnormalities similar to those of schizophrenia. This has been the starting point for the present study.

We have used the phenomenon of «latent inhibition» as paradigm. This is reproducible in both animals and humans, and refers to the fact that pre-exposure to a specific stimulus (alone and without associated consequences) gives rise to a delay in posterior associative conditioning when this same stimulus should acquire new predictive properties. More specifically, «latent inhibition of the two-way active avoidance response» implies pre-exposure of the animals to a trivial stimulus (e.g., a tone) inside the shuttlebox, and this same stimulus will be used later as the warning stimulus (CS) that will precede an electric shock (unconditioned stimulus, US) during the acquisition of an active avoidance task. Capacity to learn such task[4,5,31] will be deteriorated in the animals that have been preexposed to trivial stimulus. That is, they will show the «latent inhibition» phenomenon.

Thus, the present study aimed to evaluate if there were significant differences in latent inhibition of the two-way active avoidance response between the RHA strain and the Sprague-Dawley (SD) one, using the latter as «standard control» strain given its common use in behavioral studies and its good learning capacity of the mentioned avoidance task. According to our study hypothesis, and based on the mentioned behavioral and neurobiological profile of the RHA rats, it can be expected that this strain will have deficits to show latent inhibition compared to the SD strain.

MATERIAL AND METHODS

Subjects

The subjects used were 42 adult male rats of the RHA strain and 51 from the SD one (weight range: 440-530 g; age range: 3-4.5 months). The SD rats came from the Animal Breeding Service of the UAB, and were maintained in our laboratory for the 6 weeks prior to the onset of the ex-

Table 1 **Principal characteristics associated to the schizophrenic spectrum that differentiates the RHA rats from the RLA ones**

Effect	References
Neuropaharmacological/neurochemical aspects	
Greater levels of dopamine in nucleus accumbens after injection of amphetamine or cocaine	17, 23
Greater levels of dopamine in nucleus accumbens after sensitization to repeated injections of amphetamine or cocaine	See ref. 24; Giorgi et al. (in preparation; personal communication)
Greater locomotor sensitization after chronic injections of amphetamine or cocaine	24, 25 Guitart-Masip et al.* (in preparation)
Greater induction of stereotypes after high doses of acute apomorphine	26; Giménez-Llort et al. 2005*, in press
Greater density of dopamine D1 receptors in nucleus accumbens	27
Greater level of prefrontal dopaminergic activity (measured with different procedures) after different acute stressors.	21, 22, 27
Behavioral aspects	
Relative deficit in associative learning, as classic fear conditioning and fear potentiated startle	10, 28; Fernández-Teruel et al. (in preparation)
Relative deficit in conditioned aversion to taste	29
Relative deficit in working memory	See ref. 11 (for review); 14
Acceutuated presence of irrelevant motor responses in instrumental learning	15*, 16
Elevated locomotor activity during exposition to novelty situations (e.g., open field, activity boxes, etc.)	13, 26* Giménez-Llort et al. 2005*, in press

*In these cases, the RHA rats are also compared with the standard rat strain Sprague-Dawley (SD).

periment. They underwent an habituation process consisting in manipulation (and/or weighing) of the animals 20-21 times over this period (3-4 times per week). This procedure of habituation to manipulations was done to radically reduce the number of SD animals that show freezing behaviors to a maximum (that is, they do not escape from the electrical shock or avoid it, but remain immobilized), thus facilitating the appearance of active behaviors (crosses —escaping or avoidances— to the opposite compartment) during learning of active avoidance, in line with previous studies of our laboratory[32,33].

RHA animals come from the rat colony of this strain that has been maintained in our laboratory since 1997, so that they did not need to undergo the habituation produce administered to the SD rats. RLA strain rats *(Roman low-avoidance)* were not used due to their almost total incapacity to acquire two-way active avoidance behavior. Thus, SD rats are used (these do learn such behavior) as the RHA comparison group.

All the animals were housed in pairs of the same sex in Macrolon boxes (40×25 cm) with free access to water and food, under temperature regulated conditions (22±2 ºC), humidity (50%-70%), and 12 h light-dark cycle (turning on the light at 8 a.m.).

Procedure

Apparatuses

The experiment was conducted in three identical shuttleboxes (Letica Inst., Barcelona, Spain), located within three soundproof (and ventilated) enclosures that were independent, with a fluorescent light bulb situated behind an opaque wall of the shuttlebox that provided weak and diffuse illumination. The experimental room is maintained dark and with homogeneous background sound produced by an extractor.

The shuttleboxes are formed by two compartments of equal size (25×25×28 cm in height) connected through a door (8×10 cm, always open). A 1,000 Hz, 80-dB tone is used as conditioned stimulus (CS), while the unconditioned stimulus (US) consists in an electric shock of 0.5 mA and 30 sec. duration applied through the floor grid. In each trial, 5 seconds after initiating the CS, the US (electric shock) was initiated and the CS remained active for a maximum of 30 additional seconds (the maximum duration of the US was also 30 seconds).

Experimental session

It consisted in the two following consecutive phases:

a) Pre-exposure phase. The animals of the «npe» (not pre-exposed) groups remained in the Shuttleboxes for 8.5 minutes

(individually) without receiving any stimulation. The animals of the groups «pe15» remained in the shuttleboxes for 1 minute without receiving stimulation, after which 15 tones (identical to the CS described above) that were 5 seconds long were administered at variable intervals (randomized) between 15-45 seconds (mean interval: 30 seconds). Thus, all the experimental groups remained in the shuttleboxes for 8.5 minutes (being or not being pre-exposed to tone) before initiating the next phase (that was consecutive).

b) Learning phase. Once the pre-exposure phase ended, the 4 groups of animals immediately undertook the learning phase (acquisition of two-way active avoidance), in which 100 consecutive trials with the following characteristics were conducted: CS followed, 5 seconds later, by the US (both, CS and US overlapped for a maximum of 30 seconds). The CS and US could be ended when the animal crossed to the opposite compartment: it was an avoidance response if the crossing occurred during the first 5 seconds of the CS and an escape response if the animal crossed over when the US was already present. Once the CS or CS+US were finished, there was a variable rest interval (intertrial intowad) between 15-45 seconds (mean: 30 seconds) before the onset of the next trial (new presentation of CS).

Statistical analysis

The number of total avoidances at the 50 trials point (fig. 1A) and after completing the 100 trials (fig. 1B) were analyzed with the Student's *t* test (independent data) for each one of the rat strains.

RESULTS

In figures 1A and B, it can be observed that there are significant differences between the two SD groups both at 50 trials ($t[49] = 3.63$; $p < 0.001$) and in the total session score (100 trials ($t[49] = 2.7$; $p < 0.01$), in the sense that the «SD pe15» group had significant deterioration (latent inhibition) in the acquisition of two-way active avoidance. On the other hand, the two RHA groups do not differ either at 50 (fig. 1A) ($t[40] = 1.27$; $p > 0.2$) or at 100 trials (fig. 1B) ($t[40] = 1.56$; $p > 0.12$), demonstrating the absence of latent inhibition in the RHA rat strain under the present conditions (15 pre-exposures). The number of freezer animals (incapable of avoidance or escaping the electric shock) among the SD rats was insignificant, as was expected from the habituation procedure to the manipulations (see Materials and methods).

It must be indicated that in previous pilot studies, we have already observed latent inhibition of the active avoidance in RHA strain. The avoidance response percentages (in comparison with the «non-preexposed» control groups) ranged from 68% to 80% in preexposed groups at 60 and 30 stimuli (identical to that used in the present study) respectively. The high variability of the results in the SD comparison groups (due to the appearance of freezers in a reduced sample) prevented the effect from becoming significant in this strain (in spite of the fact that the percentages of avoidance reductions were almost identical to those of the RHA), while it was significant in the RHA rats. Thus, we decided to increase the number of animals per experimental groups in this study and to also approach threshold conditions (number of pre-exposures to the trivial stimulus so that the latent inhibition would not appear in the RHA strain). That is, hindering the appearance of latent inhibition phenomenon by reducing pre-exposure number to 15 trials.

DISCUSSION

The results of the present study are consistent with the initial hypothesis, as latent inhibition of active avoidance

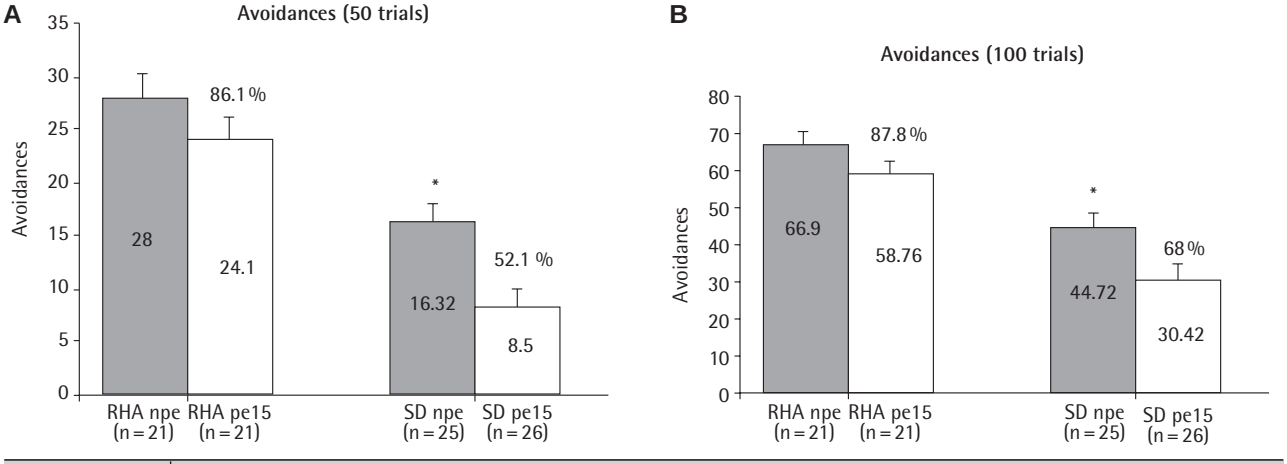

Figure 1 *Mean + standard error of avoidances in shuttlebox at 50* **(A)** *and 100 trials* **(B)** *for the RHA groups (left columns) and SD (right columns) not preexposed (npe) and 15 pre-exposures (pe15). *p < 0.001, Student's* t *test vs SD-pe15 group. The number inside the columns show the avoidance mean and the «%» on the columns show the percentage of avoidance regarding the respective «npe» groups.*

has been obtained in the SD rats. This is even more noticeable during the first 50 trials of acquisition (see figs. 1A and B). On the contrary, this phenomenon has not been observed in the RHA rats. The consistency of these results must be stressed, given the relatively high number of subjects (n = 21-26) used (in the pilot studies mentioned above, only 10-12 animals per group were used).

The results obtained, together with the pilot ones mentioned previously, suggest that the pre-exposure threshold (number of CS required pre-exposures) for latent inhibition to appear in RHA rats is higher than those required by SD animals. Future studies will aim to confirm this pre-exposure threshold, varying the number of their trials between 10 and 25 pre-exposures (given that we have observed latent inhibition in the RHA rats with 30, as has been stated). If confirmed, this latent inhibition deficit could indicate, in turn, that certain attentional filtering processes (or information processing) in the RHA are abnormal, which could be consistent with that observed in patients having schizophrenic spectrum[34].

The latent inhibition (similar to prepulse inhibition of the startle response[34]) is considered a model with construct validity of certain schizophrenic symptoms not only because a deficit in them is observed in psychotic patients but because the administration of typical and atypical antipsychotics facilitates the appearance of the phenomenon in laboratory rodents[34]. In the same way, disruption of latent inhibition induced by amphetamine or selective brain damages is also reverted by the administration of these antipsychotics[34]. On the other hand, the administration of antipsychotics (such as haloperidol and clozapine) directly to the nucleus accumbens (mesolimbic dopaminergic system) facilitaties the appearance of latent inhibition in rats[34]. The drug results mentioned thus support the idea that this animal model seems to have a reasonable predictive validity.

The presence of a latent inhibition deficit (and prepulse inhibition of the startle response) has been observed in two animal models pharmacogenetically selected due to their altered response to dopaminergic drugs, such as the APO-SUS rats (hypersensitive to apomorphine); and mice with low response to antipsychotics[35]. Similar results have been observed in the consanguineous BN (or Brown Norway)[1] rats that have not been selected by behavioral or pharmacological criteria. The three genetic models mentioned are considered as animal analogs having schizophrenia-like attentional deficits with certain construct validity. As stated previously, the RHA rats have been selected (since the end of the 1960's) by their efficiency in the acquisition of two-way active avoidance behavior, while their counterpart, the RLA strain, does not acquire such behavior[8,13]. On the other hand, in comparison with the RLA (and with SD rats, in the few cases in which the comparison has been done), the RHA rats have a combination of neurobiological and behavioral phenotypes that suggest similarities with certain aspects of schizophrenia. This is thus indicated by the mesolimbic dopaminergic hyperactivity (specifically in the nucleus accumbens; table 1[23-26]) observed in the RHA strain and its impulsiveness or incapacity of inhibiting irrelevant locomotor responses (in certain operant learning tasks (table 1) and decreased capacity to establish associative learning, especially classical conditioning of fear and conditioned aversion to taste (table 1). In addition, the RHA rats have elevated locomotor response (regarding the RLA and SD) when exposed to novelty situations[13,26] (table 1), in a similar way to the APO-SUS rat strain proposed by Ellenbroek et al.[2] as the first genetic animal model of attentional schizophrenic symptoms. The fact that a decrease in the number of NK (*Natural Killers*)[36] cells has been demonstrated in the RHA strain also seems to be consistent with that observed in the APO-SUS strain and in schizophrenic patients[2].

The RHA rat strain may thus constitute an useful model for the study of vulnerability to alterations of the schizophrenic spectrum. The deficit in the pre-exposure threshold for latent inhibition presented here needs to be confirmed. However, other measures such as mesolimbic dopaminergic hyperactivity (measured by microdialysis) and greater sensitivity to psychostimulants, locomotor hyperactivity due to novelty and difficulty in working memory tasks and aversive associative learnings presented by the RHA rats (table 1; and refs.[10,14,28,29], and Fernández-Teruel et al. in preparation), added to the present results, make it possible to anticipate a reasonable validity of such strain as a model of some attentional alterations (and associative capacity) observable in schizophrenic patients. The goodness of the model should be confirmed, however, by studies on other attentional conditions, such as prepulse inhibition of the startle response and those regarding the effects of antipsychotic drugs. Some of these studies are on-going in our laboratory.

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