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Haloperidol treatment at pre-exposure phase reduces the disturbance of latent inhibition in rats with neonatal ventral hippocampus lesions

Le traitement par l'halopéridol pendant la phase de pré-exposition réduit la perturbation de l'inhibition latente après lésion néonatale de l'hippocampe chez le rat

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ABSTRACT

Animals with neonatal ventral hippocampal lesions develop during or after adolescence abnormal behaviors related to schizophrenia such as anxiety and latent inhibition disruption. The aim of this study was to test whether haloperidol injection prior to pre-exposure session in the latent inhibition test would facilitate latent inhibition.

Lesioned animals showed a significant decrease in the number and duration of social interactions, a decrease in the marbles buried, a significant increase in locomotor activity, and a disruption of latent inhibition. In the conditioned taste aversion test, injection of haloperidol produced the recovery of latent inhibition. These findings demonstrate that neonatal lidocaine lesion of the ventral hippocampus can induce behavioral changes related to schizophrenia, and injection of haloperidol, when restricted only to a three-day pre-exposure, is sufficient to facilitate latent inhibition.

RÉSUMÉ

Les lésions néonatales de l'hippocampe ventral chez les rats provoquent des altérations comportementales, comme l'anxiété et la diminution de l'inhibition latente, deux comportements relatifs au phénotype schizophrène. Notre travail avait pour objectif de préciser l'effet facilitateur de l'halopéridol sur l'inhibition latente après son administration en phase de préexposition à la suite d'une lésion néonatale bilatérale de l'hippocampe ventral. Nos résultats montrent que les animaux lésés présentent une diminution significative aussi bien au niveau du nombre de leurs interactions sociales qu'à celui du nombre de billes enterrées. Chez ces animaux, l'activité locomotrice est largement augmentée par rapport aux témoins. Le conditionnement d'évitement a montré que la lésion altère de façon significative l'inhibition latente, qui se trouve diminuée par rapport

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au témoin. Ce résultat est confirmé par le test d'aversion gustative conditionnée. Cependant, nous avons pu montrer que l'administration d'halopéridol avant chaque session de pré-exposition permet de faciliter l'inhibition latente.

1. Introduction

Several studies have shown that schizophrenia stems from neurodevelopmental abnormalities that occur during the process of neurogenesis, neuronal migration, cell differentiation, synaptogenesis and myelination [1–5]. The ventral hippocampus, which sends prominent glutamatergic projections to the prefrontal cortex and thalamus, sites involved in the structural and functional alterations seen in schizophrenia [6–9], is a key component in the pathophysiology of this disease. In order to understand the underlying pathophysiology and pharmacological aspects of schizophrenia, various animal models have been developed. An animal model based on the neonatal lesion of the hippocampus shows a number of behavioral abnormalities related to schizophrenia such as deficit in latent inhibition [10,11], impaired social behavior [12] and hyperlocomotion in an open-field test [13]. These behavioral changes are consistent with enhanced activity of the nucleus accumbens/striatal dopaminergic system (DA) and prefrontal cortical dysfunction.

Cognitive impairment is a central manifestation of the schizophrenic illness [14]. Adult patients with schizophrenia suffer from abnormalities in attention and information processing. One type of behavioral process that has been examined in this context is latent inhibition (LI), which refers to delayed conditioning to a stimulus that has repeatedly been presented without reinforcement [15–17]. Disruption of LI, which corresponds to the failure of schizophrenics to ignore irrelevant stimuli, has received increasing attention as a viable animal model [18–23]. At present, it is not clearly understood whether the stage, the duration of illness, or the treatment by neuroleptics is responsible for these discrepancies. LI is similar in humans and animals and can be viewed as reflecting analogous processes across species [24].

The pharmacology of LI in nonhuman subjects has been investigated with aversively motivated LI procedures such as conditioned emotional response, conditioned avoidance response, conditioned taste aversion, conditioned eyeblink, and conditioned freezing (for a review, see [25]). It has been suggested that the dopaminergic system is involved in the expression of LI (difficulty of learning an association involving a pre-exposure (PE) stimulus) rather than in the acquisition of LI (the cognitive processes by which the stimulus loses its associative capacity) [26]. Some experiments have demonstrated that haloperidol could facilitate LI if it is injected before both the PE and the conditioned phase [26,27]. Thus, the timing of drug administration is a critical factor, which still needs to be clarified. Several studies have been done on the timing of drug administration by comparing the effects of dopamine manipulations during the PE phase, the conditioning phase, or both [27,28]. These studies agree that altered LI could be observed only when DA neurotransmission is manipulated during the conditioning phase [28].

The present study has two major objectives: (1) to evaluate the long-term effects of the nVH lesion by lidocaine injection in rats at postnatal day 7 and validate if this models aspects of schizophrenia, and (2) to investigate the effect of haloperidol injection at the pre-exposure phase of LI to assess dopaminergic involvement in LI and whether dopamine is a contributing factor in the expression (learning) or in the acquisition of LI (the cognitive process).

2. Material and methods

2.1. Animals

The experiments involved 20 Sprague-Dawley rats, maintained in the central animal care facility under constant temperature conditions ($20 \pm 2\,^{\circ}C$), 12 h/12 h light/dark cycle and food and water available *ad libitum*. All procedures were conducted in conformity with approved institutional protocols and with the provisions for animal care and use prescribed in the Scientific Procedures on Living Animals ACT 1986 (European Council directive: 86/609 EEC). All efforts were made to minimize animal suffering.

2.2. Surgery

At postnatal day 7 (PND7), pups were randomly separated into two groups: (1) a control group given normal saline injection (0.3 μL) and (2) a lesioned group given 1% lidocaine (Laprophan®; 0.4 μg/3 μL) injection in the ventral hippocampus. Hypothermic anesthesia was induced in the pups by placing them on ice for about 6–7 min and then secured on a Styrofoam platform mounted on a stereotaxic frame (David Kopf Instruments). An incision was made in the skin overlying the skull and 0.3 μL of Lidocaine or vehicle (0.9% NaCl) was injected bilaterally into the ventral hippocampus (AP, 2.8 mm; ML, 3.5 mm; and VD, 5.0 mm relative to bregma as defined by Lipska et al. [3]). The micosyringe was withdrawn 3 min after injection and the skin incision closed. The pups were warmed and returned to their mothers. After the weaning, the animals were housed in new cages by group and gender. Behavioral testing started on PND 56.

2.3. Validation of nVH lesion model for schizophrenia like behavior

Prior to the LI test, animals were screened for schizophrenia-related behavior and hippocampal lesioning. All behavioral testing was performed from 9 am to