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Long-term consequences of early experience on adult avoidance learning in female rats: Role of the dopaminergic system

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Abstract

Following our hypothesis that juvenile emotional and/or cognitive experience should affect learning performance at preweaning age as well as adulthood, the present study in female Wistar rats aimed to examine the impact of (i) avoidance training at preweaning age, (ii) exposure to repeated maternal separation, (iii) the combination of both, and (iv) the blockade of dopaminergic neurotransmission on adult two-way active avoidance learning in rats. We found that preweaning, i.e. three week old, rats were less capable of avoidance learning compared to adults. Our main findings revealed that preweaning avoidance training alone improved avoidance learning in adulthood. Furthermore, maternal separation alone also improved avoidance learning in preweaning and in adult rats, but this effect of maternal separation did not add up to the beneficial effect of preweaning avoidance training on adult learning. In addition, the pharmacological blockade of dopamine receptors during preweaning avoidance training via systemic application of haloperidol impaired preweaning avoidance performance in a dose-dependent manner. Testing the haloperidol-treated preweaning presumed "non-learners" as adults revealed that they still showed improved learning as adults. Taken together, our results strongly support the hypothesis that emotional as well as cognitive experience at preweaning age leaves an enduring "memory trace," which can facilitate learning in adulthood. Our pharmaco-behavioral studies suggest that unlike the adult brain, preweaning learning and memory formation is less dependent on dopaminergic mechanisms, which raises the intriguing question of possible alternative pathways.

Keywords: Haloperidol; Juvenile learning; Shuttle box; Learned helplessness

1. Introduction

There is evidence that emotional as well as cognitive experience during early childhood plays an important role in shaping neural circuitry and behavior, and may thereby determine the capacity for adult learning and memory function (Matthews & Robbins, 2003; Matthews, Wilkinson, & Robbins, 1996; Pollak, 2003; Pryce & Feldon, 2003; Shors, 2004; Weiss, Domeney, Moreau, Russig, & Feldon, 2001). Using a two-way active avoidance paradigm (TWA), the present study is based on the hypothesis that avoidance training at preweaning age (i.e., cognitive experience) should improve adult avoidance learning. Furthermore, we predicted that repeated maternal separation (i.e., juvenile emotional experience) prior to preweaning learning experience might interfere with the beneficial effect of juvenile cognitive experience on adult learning success. Additionally, in a pharmaco-behavioral approach we investigated a possible role of dopaminergic neurotransmission in preweaning as well as adult avoidance learning. The TWA paradigm was chosen because of its wide acceptance to test the impact of various parameters, such as the exposure to stress or drugs, on associative learning in adult animals

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(Arenas, Vinader-Caerols, Monleon, Parra, & Simon, 1999; Bischof, Stark, Wagner, & Scheich, 2000; Escorihuela et al., 1999; Stark, Bischof, & Scheich, 1999; Stark, Bischof, Wagner, & Scheich, 2000; Stark, Rothe, Wagner, & Scheich, 2004; van der Staay, Raaijmakers, & Kerbusch, 1983).

The predicted beneficial effect of preweaning learning experience on adult performance is supported by numerous findings in humans and animals. For example, it is long been known that exposure to language (humans) or songs (birds) during distinct developmental time windows ("sensitive periods") has a pronounced impact on speech acquisition in human infants or song learning in song birds (Kuhl, 2003; Kuhl, 2004), respectively. Recent experiments in humans highlight the importance of an intact and lively social environment as a main factor for the development of cognitive capacities, and in turn emphasize the devastating effects of social deprivation or traumatic experiences on juvenile cognitive functions (Kuhl, 2003; Kuhl, 2004). Furthermore, the critical impact of neonatal and juvenile experience on the functional maturation of learning-relevant neural circuits was recently demonstrated in barn owls, where anatomical projections acquired during juvenile association learning of auditory cues and locations in visual space persist until adulthood (Linkenhoker, von der Ohe, & Knudsen, 2005). In rats it has been shown that early experience shapes adult learning in different learning tasks (Cornwell-Jones, Velasquez, Wright, & McGaugh, 1988; Cramer, Pfister, & Haig, 1988; Gschanes, Eggenreich, Windisch, & Crailsheim, 1998). For the TWA paradigm it was shown in rats that performance is a function of age, with lower number of avoidance reactions in preweaning rats compared to adult animals (Bauer, 1978). The present study addressed the question whether, and in which way, "memory traces" from such weak preweaning learning might be stored until adulthood and thereby could improve adult learning.

The second aim of this study was to examine the interaction of juvenile emotional experience (maternal separation) *prior* to preweaning cognitive experience (avoidance training) on adult learning capacity. There is a considerable amount of literature describing the critical importance of emotional experience during childhood on cognitive development in humans and animals (Heim & Nemeroff, 2001; Pryce & Feldon, 2003), however, the existing literature remains controversial. There is accumulating evidence that, among others, the duration and/or time point of exposure to maternal separation is critical concerning its impact on the animal's adult behavior. For instance, improved adult learning performance was observed in rats which experienced daily 6-h periods of maternal separation during the third week of life (Lehmann, Stohr, & Feldon, 2000) or a single 24-h separation on postnatal day 9, whereas adult learning was impaired when the 24 h separation occurred at postnatal day 4 (Lehmann, Pryce, Bettschen, & Feldon, 1999). Additionally, a positive outcome of neonatal handling (15 min maternal separation) and early deprivation on adult TWA learning has been described (Lehmann et al., 2002; Pryce, Bettschen, Nanz-Bahr, & Feldon, 2003). Notably, most studies are focussed on the behavioral outcome displayed in adulthood, whereas little is known about the more immediate effects detectable around weaning. This is somewhat surprising, especially when considering that the search for early markers of learning and memory impairments may lead to the development of therapeutic interventions for the cure of learning disabilities as early as possible. The present study aimed to fill this gap by comparing the immediate and long-term effects of repeated maternal separation on avoidance learning in preweaning (3rd week of life) and adult rats (12th week of life), respectively.

One major advantage of animal models is the detailed identification and characterization of the neuronal mechanisms which underlie preweaning and adult learning. Therefore, the third aim of this study was to assess a possible role of dopaminergic neurotransmission in TWA learning of *preweaning* rats. Assuming that preweaning rats, in spite of their comparably low learning performance, nevertheless establish a complete or incomplete behavioral strategy and/or an association between the conditioned and the unconditioned stimulus, we asked whether this is mediated by dopaminergic mechanisms. This idea is supported by findings in adult animals, where it was shown that lesions of brain areas receiving dopaminergic projections (i.e., hypothalamus, striatum, amygdala, thalamus and hippocampus) impair the acquisition of the avoidance task (Gomita & Ueki, 1980; Guenaire & Delacour, 1983; Holahan & White, 2002). Furthermore, studies using *in vivo* microdialysis in adult Mongolian gerbils (Stark et al., 1999, 2000, 2004) elegantly demonstrated that the establishment of an avoidance strategy in a TWA task is accompanied by an increase in extracellular dopamine in the medial prefrontal cortex (mPFC). Pharmaco-behavioral studies in adult rats revealed that treatment with haloperidol, preferentially acting as a D2-receptor antagonist, induces a dose-dependent impairment of avoidance learning (Anisman & Zacharko, 1982; Arenas, Parra, & Simon, 1993; Blackburn & Phillips, 1989; Carey & Kenney, 1987). Finally, if the blockade of dopaminergic neurotransmission induces learning impairment in the preweaning animal, one should predict that these animals should not show improved learning in adulthood, since they were not able to acquire and/or transfer information or experiences from preweaning learning exposure to the adult training situation.

2. Materials and methods

2.1. Subjects

Wistar rats (strain Schönwalde) from the breeding colony at the Leibniz Institute for Neurobiology Magdeburg were used for all experiments. Pregnant females were checked for litters daily, and at the day of birth (P0) litters were standardized to 10 female pups per dam. At P21, pups from all experimental groups were weaned and housed in groups of five per cage until P80. All animals were housed in translucent plastic cages (59.5 × 20.0 × 38.0 cm; length × depth × height) under controlled laboratory conditions (temperature: 21 ± 2 °C; humidity: 55 ± 5%) with free access to food and water under an artificial 12:12 light–dark cycle (light on at 06:00 a.m.). Husbandry, comprising cage cleaning, was done once a week.