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Behavioral effects of combined environmental enrichment and chronic nicotine administration in male NMRI mice

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HIGHLIGHTS

- EE mice gained less body weight and displayed a higher fluid intake than SE mice.
- EE induces anxiolytic-like effects in the elevated plus-maze.
- EE mice displayed lower exploration and spontaneous motor activity than SE mice.
- Chronic nicotine treatment decreases motor activity but did not improve learning.
- Need to evaluate the interaction between EE and cognitive effects of nicotine.

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ABSTRACT

Environmental enrichment (EE) is an experimental paradigm which provides sensory, social, physical and cognitive stimulation for rodents. Experimental evidence indicates that this type of housing induces different neurobiological and behavioral changes. However, few studies have evaluated the consequences of combined exposure to an enriched environment and nicotine administration during a critical period of development such as adolescence. Taking into account previous studies, it can be hypothesized that a chronic treatment with nicotine would modulate the effects of rearing animals in enriched environments. In the current study, our main aim was to evaluate the effects of EE and chronic nicotine administration on physiological parameters (weight, fluid intake and cotinine levels), motor activity, exploratory behavior, anxiety and learning in male NMRI mice. Half of the mice (n = 32) were exposed to an enriched environment (EE) and the other half (n = 32) were housed in standard environments (SE) with or without oral nicotine administration (100 μg/ml). After 3 weeks, mice were evaluated in a behavioral battery that included an elevated plus-maze, a hole board, an actimeter and an inhibitory avoidance task. Blood cotinine levels were measured in an additional group of 32 mice in order to confirm nicotine intake. Results indicated that mice reared in an enriched environment gained less body weight and displayed higher fluid intake than those maintained in a standard environment. EE reduced motor activity, exploratory behavior and anxiety, whereas it enhanced inhibitory avoidance learning. In relation to the effects of chronic nicotine treatment, the data reflected a lower increase in body weight and a reduced fluid intake in nicotine-treated mice. In the elevated plus-maze, nicotine induced a reduction of total arm entries and rearings. Cotinine levels were higher in mice that received oral nicotine than in the control group. We conclude that the EE paradigm applied in this study induces physiological and behavioral changes in NMRI mice. Chronic nicotine treatment diminished motor activity displayed by mice in the elevated plus-maze but did not have significant effects on inhibitory avoidance learning. Future studies should explore in greater depth the interaction between environmental factors and nicotine administration using longer periods of EE, a wider range of doses and/or other cholinergic agonists, acute drug administration, and sequential exposure to nicotine and EE.

1. Introduction

In enriched environments, animals are provided with different stimulating objects (houses, tunnels, platforms, ropes, nesting materials, assorted colorful toys…) which are frequently changed during the experiment [1–3]. In some cases, running wheels for voluntary exercise are also introduced into the cages [4]. These objects provide visual

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and somatosensory stimulation, thus increasing the probability of exploratory behavior, stimulation and activity [1,2,5]. In addition, the number of animals housed in these environments is larger than that kept in standard cages, which offers animals more opportunities for social stimulation and interaction [1,3,5].

Different neurobiological and behavioral changes have been reported as a consequence of exposure to enriched environments. Regarding neurobiological changes, environmental enrichment (EE) promotes synaptic plasticity [6] and cognitive reserve [7], stimulates neurogenesis in the dentate gyrus of the hippocampus [3,8] and dendritic branching [9], and elevates the levels of brain-derived neurotrophic factor (BDNF) and other neurotrophic factors [10]. EE also produces variations in the shape [11] and number [12] of astrocytes. In addition, experimental evidence in animal models suggests that enriched environments offer a non-pharmacological intervention for protecting against the onset of Parkinson's [5], Alzheimer's [13,14], Huntington's disease [1] and other conditions such as Attention Deficit/Hyperactivity Disorder [15] or depression [13]. EE also attenuates the structural and functional effects of different brain lesions [16,17] and strokes [18].

In the context of behavioral changes, it has been reported that rearing rats in an enriched environment reduces anxiety levels and improves emotional stability [19], accelerates habituation to new environments [20,21], enhances social play behavior [22], increases hot-plate latencies and reduces aggression [23], although contradictory results do exist. Exposure to an EE may also aid recovery from different stressors [24]. An improvement in a variety of hippocampal-dependent memory tasks after exposure to EE conditions has been confirmed in numerous studies in both young [25,26] and old rodents [27,28]. This improvement has been related to the sensory, physical and cognitive stimulation provided by enriched environments and the increased social interaction that this encourages [26,28].

Recently, the need has been stressed for further research regarding the interaction between EE and pharmacological manipulation [15,29]. The role of environment in the regulation of behavior and in the effects of different drugs has also been underscored lately [30–32] as a result of the hypothesis which holds that EE plays a protective role against the development of addiction to different drugs of abuse [13,29,31,33–35]. Few studies, however, have evaluated the consequences of combined exposure to an enriched environment and nicotine administration. Nicotine is the primary substance involved in tobacco addiction [36], and its behavioral and physiological effects have been widely evaluated in animals and humans. The results of such studies suggest that nicotine improves cognitive function [37] and that EE modulates some motor and neurochemical effects of nicotine in rodents [38], although these effects seems to depend on factors such as age and sex [39–41], or dosage and route of administration [42–44]. Rats housed in an enriched environment have been reported to show less sensitivity to the stimulant effects of nicotine [45] and to exhibit alterations in cholinergic receptors associated with the hyperactivity produced by this drug [38]. Nicotine also blocks the increase in dendritic branching in the nucleus accumbens related to EE [46]. Additionally, Zhu et al. [47] observed an increased release of dopamine in the medial prefrontal cortex area in animals housed in an enriched environment and treated with nicotine. Many studies have attempted to shed light on the genetic and molecular factors involved in nicotine addiction, but very little work has been carried out in order to clarify the influence of environmental factors associated with the progression of addiction to this substance [13,29,34]. A deeper understanding of the role of environmental factors in vulnerability to addiction is critical if strategies for prevention and treatment are to be effective [29,34,48]. The current lack of data concerning the combined use of nicotine and EE is an obstacle to determining the effects of environmental manipulation on behavioral responses to this drug.

Different studies have revealed that negative and stressful experiences during early life can induce structural and functional changes in the brain that encourage the consumption of drugs of abuse during adolescence and adulthood [49,50]. Previous data show that exposure to enriched environments during critical stages of development, such as adolescence, enhances the effects of EE and can reduce an individual's susceptibility to developing neurological diseases and mental disorders [13,51] as well as addiction [29,50]. In the light of previous studies of the behavioral effects of enriched environments and the relevance of being reared in this type of environment during early life, and taking into account previous research about the emotional and cognitive effects of nicotine [37], especially during adolescence, it can be hypothesized nicotine would modulate the effects of EE in the performance of different behavioral tests. The present study was conducted in order to evaluate whether or not the effects of EE are modulated by exposure to chronic oral nicotine during a critical period of development. We set out to explore the effects of EE combined with chronic treatment with nicotine on locomotor activity, exploration, anxiety and learning.

2. Material and methods

2.1. Animals

Ninety six male mice of the outbred stock Crl:NMRI (Han) were used in the current study. Mice were obtained from Charles River (Barcelona, Spain) at 21 days of age and weighing between 10 and 12 g and were housed in controlled facilities. Sixty-four of these animals were used in order to assess behavioral and physiological parameters and the other thirty two were employed to obtain blood samples. After an eight-day period of adaptation to the laboratory, half of the mice were exposed to an enriched environment (EE) and the other half remained in standard cages (SE) until the behavioral tasks were performed. Since NMRI mice are nocturnal rodents and their level of activity increases during the dark phase of their circadian rhythm [52], standardized conditions with a reversed 12 h light/dark cycle (lights on: 19:30 h) were maintained in a room with constant temperature (20–24 °C) and humidity (55 ± 10%). This procedure has been applied in other studies employing enriched environments [53–55]. All animals were allowed free access to food (Tekald Global Rodent Diet, supplied by Harlan) and water.

Experimental procedures were approved by the local ethical committee (University of Valencia) and complied with national (Real Decreto 1201/2005, de 10 de Octubre) and international guidelines (European Community's Council Directive of November 24, 1986 — 86/609/EEC) for the care and handling of animals.

2.2. Procedures and apparatuses

2.2.1. Housing conditions

At 28 days of age, mice were randomly assigned to one of two housing conditions (Enriched or Standard). On this day, baseline hole board activity was measured and data indicated that there were no significant differences between groups in the total number of head-dips. This factor was taken into account in order to avoid individual differences in basal exploratory behavior [60], which may influence preference or use of the objects present in the enriched environments. Both groups also had a comparable mean body weight at the beginning of the study [61,62].

Mice were maintained in enriched or standard conditions for 3 weeks before behavioral testing began. In the standard environment, mice were housed in groups of 4 in standard cages (42 × 26 × 14 cm) containing only sawdust. In the enriched environment, mice were housed in groups of 8 in larger cages (55 × 36 × 19 cm) that contained fixed objects (a running wheel, a colored plastic tunnel and an igloo), and an assortment of changeable toys (five per cage) and sawdust. Handling procedures were similar for both enriched and control mice. All cages were cleaned once per week and mice were weighed during the cleaning process. In the enriched cages, toys and objects were changed twice per week in order to encourage exploration and enhance the novelty of the environment [5]: once when the sawdust was changed, and a