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Involvement of D1 and D2 dopamine receptors in the antidepressant-like effects of selegiline in maternal separation model of mouse

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HIGHLIGHTS

- Maternal separation (MS) provoked depressive-like behaviors
- Selegiline exerted antidepressant-like effects in MS mice
- Effect of selegiline on the passive behaviors is mediated via D1 receptor
- D2 receptor mediated effect of selegiline on the hedonic difficulties
- Effect of selegiline on the self-care problems is mediated via both D1 and D2 receptors

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ABSTRACT

Mother-infant interactions are known to be associated with the psychological well-being of an individual in adulthood. It is well accepted that emotional stress in early life, such as maternal separation (MS), leads to alterations in the neurotransmission systems of various brain regions, especially the mesolimbic dopaminergic system, and subsequently can increase the risk for development of psychiatric disorders including depression in adulthood. Selegiline is an irreversible monoamine oxidase (MAO) type B inhibitor which increases striatal dopamine levels and exerts an antidepressant effect. In this study, 180 min of MS stress was applied to mice at postnatal day (PND) 2–14 followed by behavioral tests for determining depressive-like behaviors, such as forced swimming test (FST), splash test and sucrose preference test (SPT) in adult mice (PND 50). The open field test (OFT) also was applied to validate FST results. We used SCH23390 (D1 antagonist) and sulpiride (D2 antagonist) in order to determine the role of D1 and D2 dopamine receptors in antidepressant-like effects of selegiline. Our results revealed that MS provoked depressive-like behaviors in adult male mice, and the administration of selegiline attenuated depressive-like behaviors in MS mice. Our findings showed that D1 dopamine receptors facilitate the positive effects of selegiline on the passive behavior in the FST. Furthermore, antidepressant effects of selegiline on hedonic difficulties are mediated via D2 receptor in the SPT. The results of the splash test revealed that both D1 and D2 receptors mediate the protective effect of selegiline against motivational and self-care problems. Based on our results, we conclude that both D1 and D2 dopamine receptors are involved in mediating the antidepressant-like effect of selegiline. We found that D1 receptors mediate an effect on despair behavior, D2 receptors mediate an effect on anhedonia, and both D1 and D2 receptors contribute to the protective effects of selegiline on motivational complications.

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1. Introduction

Social environments, especially mother-infant synchrony during childhood, have a critical role in shaping the brain and behavior [1]. Previous studies have demonstrated that the quality of early life is strongly associated with psychological well-being in adulthood [2,3]. Adversity in the neonatal stage of life dramatically disturbs neuronal and brain development and subsequently affects an infant's physical and/or psychological health [4,5]. Growing body of evidence indicates that exposure to stress, especially during the neonatal period, enhances the risk of neuropsychiatric states, including mood and depressive disorders in later life [6,7]. In this regard, it has been shown that experiencing early psychological stress such as maternal separation (MS) through alterations in neurotransmission in various regions of the brain induces psychiatric disorders, including depression [8–10].

Aversive emotional experience during infancy negatively impacts the structural and functional development of limbic brain circuits [11]. Maternal care, such as licking and grooming, stimulates the developing mesolimbic dopaminergic system which leads to an increase in dopamine levels as well as dopaminergic receptors [12]. In this regard, it is well-known that MS leads to neurotransmitter changes in the brain especially in the mesocorticolimbic dopamine neurotransmission [13–15]. Maternal separation stress has been shown to induce potentially enduring changes in the density of dopamine receptors as well as lasting derangements in dopamine neurotransmission in the brain [3,14]. Previous studies have demonstrated that MS affects dopaminergic circuits through an increase in levels of glucocorticoids (GC) [16,17].

Dopamine is an important neurotransmitter involved in a number of brain functions such as emotion, reward and behavior, as well as the neuropsychiatric disorders such as depression [18] [19,20]. Depressive disorder is a debilitating mental disorder with high prevalence, morbidity, and costly socioeconomic burden [21]. Anhedonia and motivational impairments are major symptoms of depressive disorder which are associated with reward pathway deregulations. It has been shown that dopamine is associated with motivation, reward and hedonia states. Therefore, increasing dopamine levels may be considered as an avenue for the treatment of depression [19,22,23]. It has been well established that dopamine agonists improve depressive symptoms [24]. In this regard, ample evidence suggested that dopamine D1 receptor mediated the effects of antidepressant drugs in the forced swim test (FST), while other studies demonstrated that dopamine D2 receptor antagonists blocked the effect of antidepressant drugs in the FST [25,26].

Selegiline [(−)-deprenyl] is an irreversible monoamine oxidase (MAO) type B inhibitor, an enzyme involved in dopamine metabolism [27]. It has been shown that selegiline increased striatal dopamine levels, and significantly improved a whole variety of depressive symptomatologies [28]. Since selegiline is metabolized to (−)-methamphetamine and (−)-amphetamine, the effects of drug on dopamine levels in the brain may be due to its amphetamine-like action [29]. Considering that selegiline possesses antidepressant effects and also potentiates the effects of antidepressants, there could be possible uses for selegiline in the management of resistant depression [30–32].

Although selegiline has antidepressant effects by increasing the striatal dopamine levels, role of D1 and D2 dopaminergic receptors are ambiguous in these effects. Using MS paradigm, this study aimed to explore the role of D1 and D2 receptors in the behavioral tests relevant to depressive-like behaviors in male mice.

2. Materials and methods

2.1. Animals

Pregnant NMRI mice (Pasteur Institute, Tehran, Iran) were used in this study. Animals were maintained under standard laboratory conditions (12-h light/dark cycle, temperature (22 ± 1 °C) and free access to food and water). The day of birth was considered as postnatal day 0 (PND 0). The litters were subsequently assigned to the MS paradigm. In this regard, pups were briefly handled and separated from their mothers for 180 min daily during PND 2 to PND 14, beginning at 09:00 a.m. [33,34]. At the end of the separation period pups were returned to the nest cage. At PND 21, male offspring were housed in groups until experiment day PND 50.

All procedures in this study were carried out in accordance with the National Institutes of Health (NIH) Guide for the Care and Use of Laboratory Animals (NIH publication # 80-23) and institutional guidelines for animal care and use (Department of Pharmacology, School of Medicine, TUMS). All experiments were conducted between 10:00 a.m. and 02:00 p.m. Each experimental group consisted of 6 to 8 animals.

2.2. Drugs

The drugs used in this study were as follows: 1) selegiline hydrochloride: MAO-B inhibitor, 2) sulpiride (SULP): dopamine D2 receptor antagonist, and 3) SCH 23390 (SCH): dopamine D1 receptor antagonist. All drugs were purchased from Sigma, St Louis, MO, USA. All drugs were dissolved in 0.9% saline in a volume of 10 ml/kg. SULP and SCH were administered intraperitoneally (i.p.), whereas selegiline hydrochloride was administered via subcutaneous route (s.c) injections. Doses of each drug were selected based on previous published studies by Binfaré et al. and Shimazu et al. [25,35] and our own pilot studies. We treated mice with selegiline hydrocloride (60 min), SULP and SCH (90 min) prior to behavioral experiments. Dosing calculations were determined using the weight of the compound (including its salt). The dose of each drug was adjusted according to animal body weight (mg of drug/kg of body weight of mice).

2.3. Study design

Behavioral experiments consisted of open field test (OFT), forced swimming test (FST), splash test and sucrose preference test (SPT) which were conducted using control or MS mice as follows:

Experiment 1 tested the effects of the early stress experience, MS, on the different behavioral tasks related to assessing depressive-like behaviors.

Experiment 2 examined the effect of selegiline hydrochloride (1, 3, and 5 mg/kg) on depressive-like behaviors using behavioral tasks. Animals in this experiment received selegiline hydrochloride 60 min before the behavioral tests.

In experiment 3, we examined the effect of selegiline hydrochloride (3 mg/kg) along with SCH (0.03 mg/kg) or SULP (50 mg/kg) on depressive-like behaviors by using behavioral tasks. Animals in this trial received SCH or SULP 30 min prior to selegiline injection and 90 min before the tests.

2.4. Forced swimming test (FST)

The FST was carried out according to the previously described method by Porsolt et al. and Cryan et al. [36,37]. In this behavioral test, extended immobility time represents despair behavior reflecting depressive-like symptoms. Mice were separately placed in an open cylinder-shaped flask (diameter 10 cm, height 25 cm), containing 19 cm water at 23 ± 1 °C. Mice were permitted to swim for 6 min and the period of immobility was recorded throughout the last 4 min of the test. Each mouse was judged to be immobile when it ceased struggling and stayed floating motionless in the water and making only those movements necessary to keep its head above water.

2.5. Open field test (OFT)

The OFT was used to illuminate the effects of MS and treatments on motor function, exploratory behavior, and to rule out possible alterations in locomotion that might affect FST [38]. The OFT apparatus