



Research paper

Hyperforin alleviates mood deficits of adult rats suffered from early separation

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HIGHLIGHTS

- Early separation from rat parents can lead to the mood deficits and depression.
- Hyperforin, active constituent of *Hypericum perforatum*, potentially alleviates anxiety behavior.
- Hyperforin abolishes depressive symptoms evoked by early separation.

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ABSTRACT

In this study, we aimed to explore the effect of hyperforin (Hyp) on adult rats suffered from early separation. Wistar infant rats were randomly divided into three groups: control group (CON), early separation from parents group (ESP), and early separation from parents + treatment with 3 mg/kg/day Hyp group (ESP + Hyp). Postnatal rats of ESP group and ESP + Hyp group were separated from their mothers for 6 h every day on the 14th day after birth, and this separation lasted for 3 weeks, while rats of CON group had no separation. Hyperforin was intragastric administrated on the 21th day after birth, and lasted for 2 weeks in ESP + Hyp group. After separation, adult rats were evaluated by using the open field test (OFT), novelty suppressed feeding test (NSF) and forced swimming test (FST). In OFT, time spent in central grids was much shorter in ESP group compared with that of CON group. After treatment with hyperforin, time spent in central area was much longer compared with that of ESP group. In NSF, the feeding latency of ESP group was much longer than that of CON group. After treatment with hyperforin, the feeding latency was shorter compared with that of ESP group. In FST, score of ESP group was markedly higher than that of CON group. Interestingly, the score was obviously lower in ESP + Hyp group than that of ESP group. In conclusion, these results suggest that hyperforin is able to alleviate anxiety and remit depression in ESP rats.

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1. Introduction

With the rapid development of economy and the increasing of life pressure, many parents have to be separated with their children for short or long time in China [1,2]. Especially in rural areas, there were nearly 20 million left behind children, which may lead to many social issues [1]. It is well known that security, nurturance and emotional attachment play an important role in early life, any disruption of security, nurturance and emotional attachment may contribute to juveniles' subsequent difficulty in

developing warmth and relating to others. Evidences indicate that high psychopathy scores usually result from physical neglect and a disrupted family in children and adolescent [3,4]. Moreover, separation from parents also foretells psychopathic character in juvenile offender [5]. Recently, rat model subjected to the early maternal separation has been widely used to investigate this disease [5]. Many experimental protocols for maternal separation utilize both short periods (3–15 min) of maternal separation, and longer periods (often >180 min) of separation [5]. Studies report that short periods (3–15 min) of maternal separation are too short to make a serious deprivation for newborn rat [6], in contrast, the longer periods (> 180 min) of separation usually lead to a serious deprivation of rats [5]. A variety of long-term neurochemical, hormonal and behavioral changes have been observed after short and prolonged periods of maternal separation, such as the impairment of

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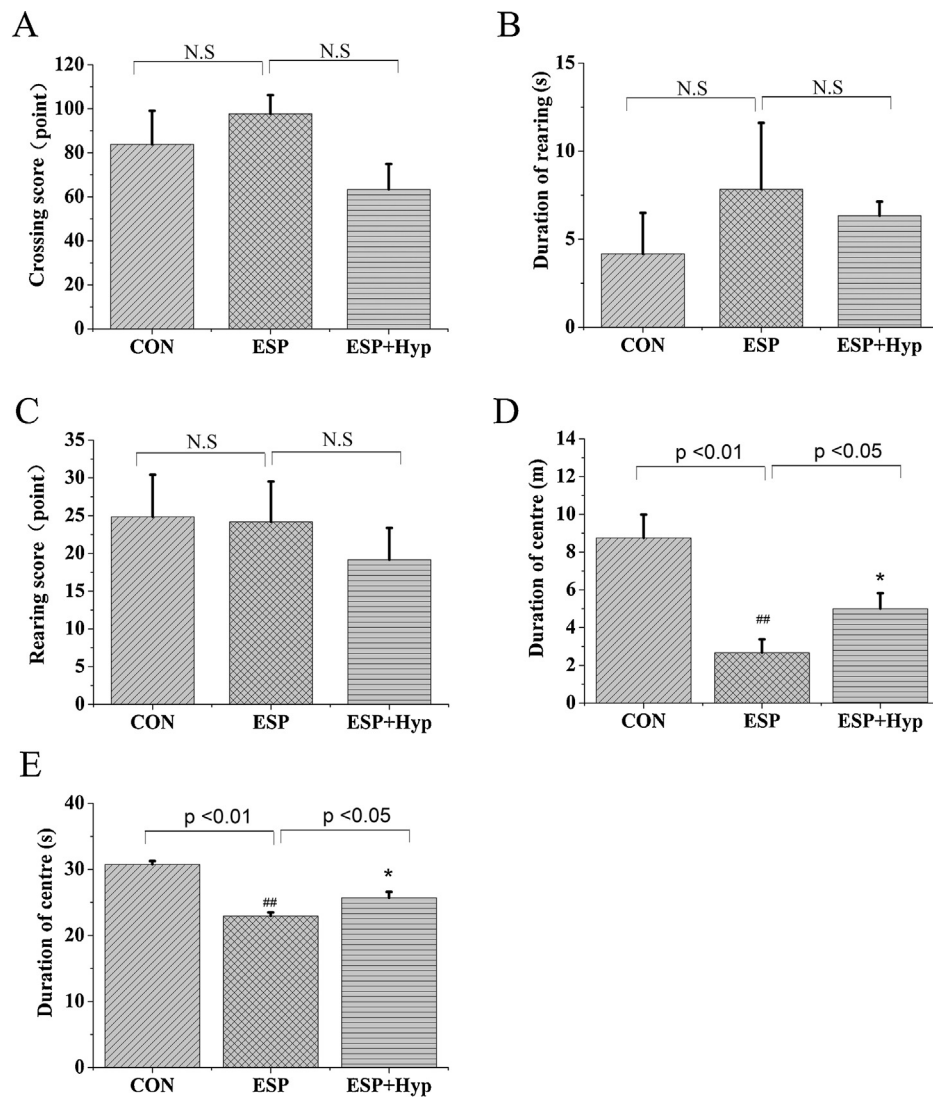


Fig. 1. Effects of hyperforin on ESP rats in open field test. (A) Crossing score; (B) duration of rearing; (C) rearing score; (D) duration of central area in distance; and (E) duration of central area in time. Data are expressed as mean \pm S.E.M. ## $p < 0.01$ comparison between CON group and ESP group. * $p < 0.05$ comparison between ESP group and ESP + Hyp group. N.S indicates no significant difference.

reversal learning and spatial learning, anxiety, play-fighting, and the unnormal metabolism of 5-hydroxytryptamine (5-HT) *etc.* [6–8]. However, the pathogenesis of this psychopathic character is still not fully understood, and there is few drug licensed for the treatment of it.

Hypericum perforatum (St. John's wort) is a traditional herbal medicine for treatment of infections and inflammatory diseases and skin wounds [9]. Recently, it has also been used for psychiatric disorders (such as depressive moods, anxiety and nervous unrest), especially for the mild to moderate depression, which causes less side effects than other used antidepressants [9]. Hyperforin is the active constituent of *H. perforatum* responsible for its anti-depressant effect, and is a phloroglucinol derivative [9]. Hyperforin is able to reduce the reuptake of 5-HT and norepinephrine (NE) by increasing intracellular Na^+ concentration through the activation of non-selective cationic TRPC6 channels [10]. Studies report that hyperforin is considered as antidepressant to alleviate the behavioral despair and learned helplessness of adult rats [11]. Besides that, several of its biological effects has also been described, including *N*-methyl-D-aspartic acid (NMDA) receptor antagonism, anti-bacteria, inhibiting proliferation of cancer cell, antioxidant, and anti-inflammatory properties [12]. However, there are few

reports about the effect of hyperforin on early separation rats. The aim of our study was to determine whether hyperforin provided anti-depressant effect on rats of early maternal separation.

2. Materials and methods

2.1. Animal care

We purchased adult pregnant female Wistar rats from the Laboratory Animal Center, Academy of Military Medical Science of People's Liberation Army, and they were singly housed under a 12 h light–dark cycle with food and water available. All animal experiments were approved by the Animal Research Ethics Committee, School of Medicine, Nankai University. In addition, all animal experiments were performed in accordance with the Animal Management Rules of the Ministry of Health of the People's Republic of China.

2.2. Early separation

The early separation experiment was performed as Eiland et al. reported [13]. Two weeks after delivery, pups were weaned and

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