Establishment of Depression Behavioral Criteria in Cynomolgus Monkeys

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Depression is a common mental disorder with relatively high lifetime prevalence and substantial disability, especially in women [1–3]. Clinical manifestations of depression include loss of interest or pleasure, disturbed sleep or appetite, poor concentration, etc., worst of which is suicide. To solve such an important global public health issue, it is essential to establish ideal animal models for study and treatment of depression. Cynomolgus monkeys have been proved to be advantageous for modeling human depression through mother–infant separation [4] and social subordination stress [5].

Behavioral tests have been performed in animals to test severity of depression and successfulness of modeling, for example, forced swim test and tail suspension test for rodents [6,7] and sucrose intake test for nonhuman primates [8]. In this study, we attempted to establish several behavioral criteria that can be easily measured to distinguish depression in cynomolgus monkeys.

After a fourteen-month observation in groups, six socially subordinate female cynomolgus monkeys and six socially dominant counterparts were chosen as depressed models and alert controls, respectively, based on their social status hierarchy (Figure 1). The subordinate and dominant monkeys came from six and four groups, respectively, and each group consisted of 14–26 monkeys. The monkeys were 6–10 years of age and housed alone in adjacent cages separated with transparent plexiglass. All the monkeys were provided by Suzhou Xishan Zhongke Lab Animal Ltd (Suzhou, China) and received humane care.

In this study, body weight, food consumption, preference for sucrose water, attempts for apple, and time of depressed posture were measured. Data are expressed as mean $\pm$ SEM and analyzed with unpaired *t*-test. $P < 0.05$ was considered statistically significant. The body weight of depressed monkeys was significantly lower than that of nondepressed monkeys

(3.03 ± 0.07 vs. 3.57 ± 0.13 kg, $P < 0.01$; Figure 2A). Food consumption relative to body weight was calculated as the mean of 3-day measurements. Our results showed that depressed monkeys ate more food than the nondepressed (40.76 ± 2.76 vs. 18.25 ± 0.86 g/kg, $P < 0.01$; Figure 2B). The monkeys were deprived of water for 23 h and obliged to drink from two bottles containing pure water at the 24th h. After a 3-day adaptation, pure water was changed to 1.5% sucrose water in one bottle and then consumption of both kinds of water was recorded for 3 days. Preference of sucrose water was calculated as the percentage of sucrose water intake to total water intake. Depressed monkeys exhibited less preference for sucrose as compared to nondepressed monkeys ($51.5 \pm 12.6\%$ vs. $81.0 \pm 2.9\%$, $P < 0.05$; Figure 2C).

Apples were given to monkeys in the cages for 3 days and then put out of the cages. Distance between the wall of the cage and the apple was a bit longer than the length of the monkey's arm. Monkeys could stretch their arms through the meshes of the cage wall. Times of reaching for apple were counted for 15 min on 3 days. Attempts for apple were calculated as times of reaching for apple in 15 min. Depressed monkeys showed more attempts for apple than nondepressed monkeys, however, without a statistical significance (Figure 2D). Depressed posture was defined as a slumped or collapsed body posture [9,10]. Behavior was recorded for 15 min during 14:00–16:00 on 3 days, avoiding feeding period. Time of depressed posture was calculated as the percentage of time keeping slumped or collapsed body posture to 15 min. Depressed monkeys spent more time in depressed posture than nondepressed monkeys ($57.3 \pm 10.1\%$ vs. $19.4 \pm 10.2\%$, $P < 0.05$; Figure 2E).

Most of our results were consistent with results of the previous study [5,8]. Interestingly, food consumption and attempts for

Figure 1 A depressed monkey beside a normal alert monkey. The normal alert monkey is attentive and alert, whereas the depressed monkey is inattentive and in a slumped posture, with open eyes in a downward gaze.

Figure 2 Behavioral criteria of depression for cynomolgus monkeys. Body weight (A), food consumption (B), preference for sucrose water (C), attempts for apple (D), and time of depressed posture (E) were measured in socially subordinate female cynomolgus monkeys and socially dominant counterparts. $N = 6$ in each group. * $P < 0.05$, ** $P < 0.01$ versus nondepressed monkey.

apple were more in depressed monkeys. It might be explained by the fact that depressed monkeys distinguished according to their social status hierarchy could not obtain enough food when in groups, and when housed alone, they ate more food and fruits as compensation.

In conclusion, body weight, food consumption, preference for sucrose water and time of depressed posture may be ideal criteria to distinguish depression in cynomolgus monkeys. However, whether attempts for apple also can be a criterion needs further researches.

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Conflict of Interest

The authors declare no conflict of interest.

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