MODELING DEPRESSION IN RATS: CHRONIC CORTICOSTERONE ADMINISTRATION AS A TOOL FOR ANTIDEPRESSANT EFFICACY ASSESSMENT

Ewald Auer, Aaron Fantina-Woblistin, Livia Breznik, Magdalena Daurer, Stefanie Flunkert, Manuela Prokesch

Scantox Neuro GmbH, Parkring 12, 8074 Grambach, Austria

scantox

For further information and inquiries contact office-austria@scantox.com

BACKGROUND

Depression is a prevalent mental illness that affects approximately 280 million people worldwide. The aetiology and pathogenesis of depression is still poorly understood; however, it is often preceded by prolonged periods of stress.

We examined the effects of chronic treatment with corticosterone, a rodent´s stress hormone, on depressive-like symptoms in rats and investigated whether observed changes can be reversed by anti-depressant fluoxetine.

MATERIALS and METHODS

Wistar rats (9 weeks, n=8) were treated with corticosterone (CORT) or vehicle via drinking water (DW) or subcutaneous (s.c.) injection daily for 30 days. As a reference item, fluoxetine or vehicle were administered via intraperitoneal injection, also for 30 days. Sucrose preference test (SPT), open field test (OF), elevated plus maze (EPM), forced swim test (FST), grooming behavior (GB), coat scoring (CS) and passive avoidance (PA) were used to test for depression-related phenotypes.

In addition, serotonin and corticosterone measurements in plasma, as well as histological evaluations in the animals' brain are planned.

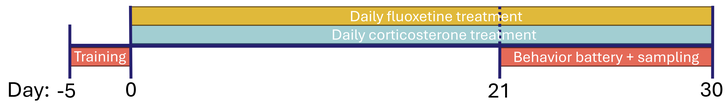
Results

Preliminary analysis of first cohorts show a clear difference in CORT treatment mode; with s.c. route of administration showing a more pronounced phenotype. Focusing on the s.c. study arm, results in CS and GB show a less thorough grooming and increased time to initiate self grooming. However, SPT did not reveal a reduced sucrose intake. Although OF did not show significant differences, a trend for reduced exploratory behavior could be observed in CORT-treated animals and effect size analysis indicates biological difference. FST showed a reduced mobility and an increased immobile phase. Additionally, fluoxetine used as a positive control led to severe adverse gut disturbances and weight loss, while not ameliorating CORT treatment effects.

CONCLUSION

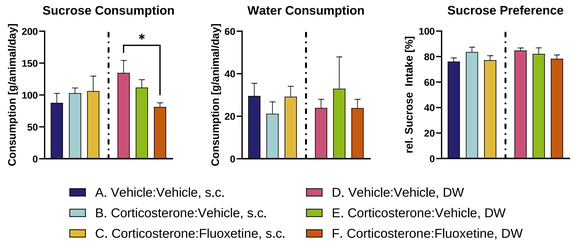
Taken together, our preliminary data indicate increased efficacy of s.c. CORT treatment over DW application. Behavioral data show higher levels of lethargy and signs of helplessness in combination with reduced self-care.

Outline



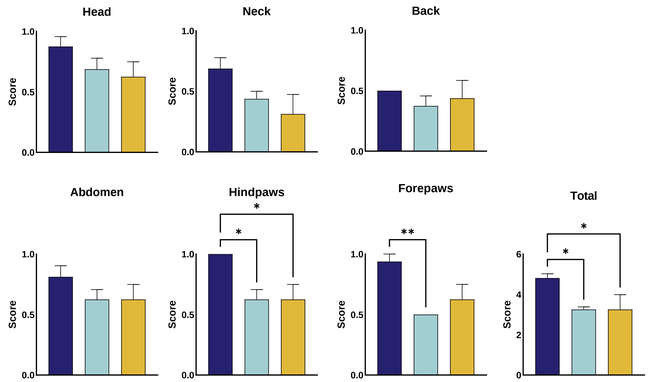
▲ **Figure 1: Outline of experimental setup.** After 5 days of SPT training, rats were treated for 21 days with vehicle, corticosterone, or corticosterone and fluoxetine. From day 21 onwards, various behavioral test were performed while treatment continued. Behavioral testing was always performed at the same time of the day. Animals were sacrificed on day 30.

Sucrose Preference



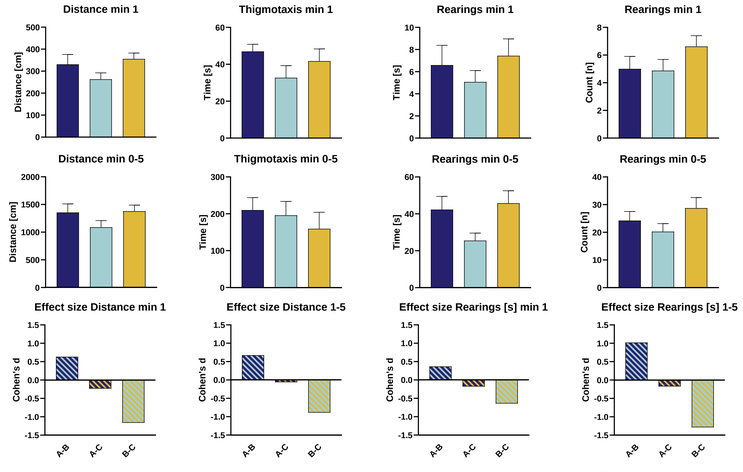
▲ **Figure 2: No difference in sucrose preference between vehicle- and corticosterone-treated animals.** Before treatment, animals underwent 5 days of SPT training. After 21 days of treatment by s.c. injection or DW, sucrose preference was evaluated by the consumption rate of sucrose solution or water, available *ad libitum* for 24 h. Mean + SEM. One –way ANOVA or Kruskal Wallis test followed by Dunnett's or Dunn's *post hoc* test, respectively. *p<0.05.

Coat Score



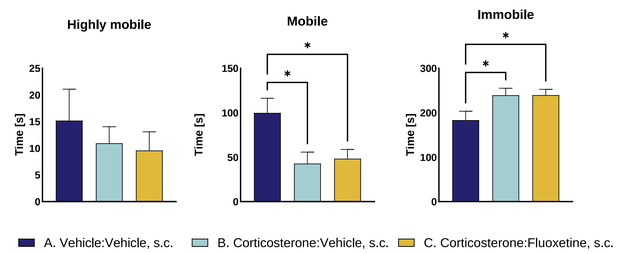
◀ **Figure 3: Coat scoring shows significant differences in self-care behavior in the home cage**. Animals were treated according to their group and 1 h later, coat tidiness at the head, neck, back, abdomen, hindpaws, and forepaws was evaluated by scoring them either 1 (well groomed), 0.5 (moderately groomed), and 0 (unkempt). Total represents the sum of all scores. Mean + SEM. Kruskal Wallis followed by Dunn's *post hoc* test. *p<0.05, **p<0.01.

Open Field



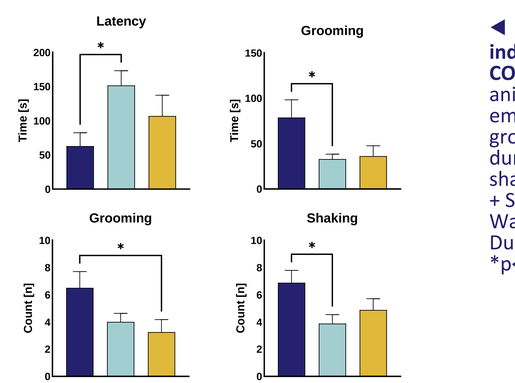
◀ **Figure 4: Open field test showing a trend for lower activity in the first minutes of testing**. The open field test was performed after coat scoring and the distance traveled, thigmotaxis, as well as rearing time and events were recorded over 15 min of testing. Additionally, the effect size analysis was performed to evaluate biological effects. Mean + SEM. One –way ANOVA.

Forced Swim Test



◀ **Figure 5: Forced swim test showing significantly higher learned helplessness indicators in CORT-treated animals**. Animals were transferred to a cylinder filled with water without a means of escape for 15 min. On the same day, animals were place in the cylinder again and filmed for 5 min. Lethargy was evaluated by measuring mobility and immobility metrics. Mean + SEM. One –way ANOVA followed by Dunnett's *post hoc* test. *p<0.05.

Grooming



◀ **Figure 6: Grooming behavior indicating increased lethargy in CORT-treated animals**. After the FST, animals were transferred to an empty cage and the latency to first grooming behavior, grooming duration and events, as well as shaking events were recorded. Mean + SEM. One –way ANOVA or Kruskal Wallis test followed by Dunnett's or Dunn's *post hoc* test, respectively. *p<0.05.