Effects of empagliflozin and L-ornithine L-aspartate on behaviour, cognitive function, and physical performance in mice with non-alcoholic steatohepatitis

V. PRIKHODKO, Y. SYSOEY1,2, S. OKOVITYI

1. Saint Petersburg State Chemical Pharmaceutical University, Saint Petersburg, Russia
2. Institute of Translational Biomedicine, Saint Petersburg, Russia

INTRODUCTION

- non-alcoholic fatty liver disease (NAFLD) has a number of extrahepatic complications, which include cerebrovascular disease, cognitive and behavioural alterations, and accelerated brain aging
- patients with NAFLD are at a 4 times higher risk to develop cognitive impairment, and tend to have decreased physical performance

AIM

- to evaluate the effects of empagliflozin (EMPA) and L-ornithine L-aspartate (LOLA) on cognitive function and physical performance in a mouse model of non-alcoholic steatohepatitis (NASH)

METHODS

Experimental groups: C57BL/6 male mice

- Intact (I)
  - 0.9% NaCl q.d. p.o.
  - n = 10
- Control (C)
  - NASH (0.9% NaCl q.d. p.o.)
  - EMPA
  - NASH + 2 mg/kg EMPA q.d. p.o.
  - LOLA
  - NASH + 1.5 g/kg LOLA q.d. p.o.
  - n = 14
- NASH induction:
  - a western diet, + weekly intraperitoneal carbon tetrachloride (0.32 mg/kg) for 6 months

Cognitive function assessment:
- open field (OF) test
- elevated plus maze (EPM)
- Barnes maze (BM)
- light/dark box (LDB) test

Physical performance assessment:
- weight-loaded (7.5% of b.w.) forced swim (FS) test
- triple weight-loaded exhaustive swim (TES) test

RESULTS

Animal survival
The mean lethality rate was 45.2% among all NASH groups and was not affected significantly by either of the drugs (Fig. 1).

NASH-related cognitive impairment and memory deficit
Control mice exhibited decreased movement speed (p<0.01) and increased total freezing time (p<0.01) and the numbers of head dips (p<0.05) and rearing episodes (p<0.05) in the OF, EPM, and LDB tests, indicating anxiety-like behaviour (Figs. 2-4). Control mice also had higher error percentages and latencies to find the target hole (p<0.05) on Day 12 vs. Day 5 compared to Intact animals, indicating a spatial memory retention deficit (Fig. 5).

EPM increased the number of grooming bouts and time spent in the light chamber of the LDB (p<0.05), and LOLA increased the time spent in the open arms of the EPM (p<0.05) (Figs. 2-4). The spatial memory deficit was partially rescued by both EMPA and LOLA (Fig. 5).

NASH-related decrease in physical performance
Control mice had poorer performance than Intact specimens (p<0.05, p<0.01) in both swimming tests. LOLA restored normal performance levels in the FS test, and improved post-exercise recovery (p<0.01) at 45 min after the start in the TES test (Fig. 6).

CONCLUSIONS

- experimentally induced NASH causes anxiety-like behaviour, impairs long-term memory, and decreases physical performance in C57BL/6 mice
- daily administration of EMPA (2 mg/kg) or LOLA (1.5 g/kg) ameliorates NASH-related cognitive deficit
- daily administration of LOLA also improves physical performance and post-exercise recovery

REFERENCES

1. Colognesi M et al. Depression and cognitive impairment - extrahepatic manifestations of NAFLD and NASH. Biomedicines 2020;8(7):77-86

CONTACT INFORMATION

veronika.prihodko@pharminnotech.com
Veronika A. Prihodko
Department of Pharmacology and Clinical Pharmacology
Saint Petersburg State Chemical Pharmaceutical University
197022 Saint Petersburg, Russia