The Effect of Peripheral Lipopolysaccharide Treatment on Depressive-Like Behavior of Serotonin Transporter Knockout Mice

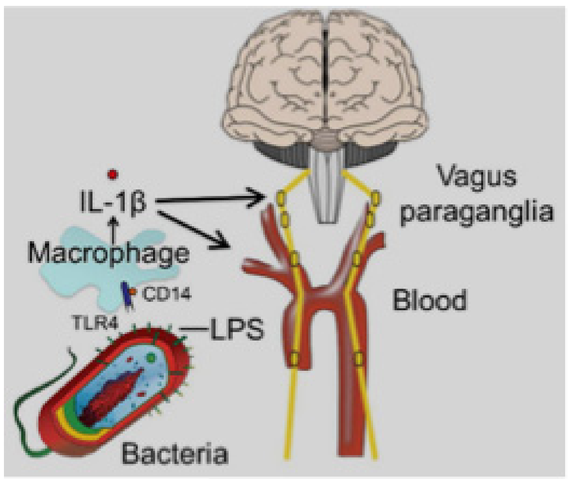
College of Veterinary Medicine
University of Missouri

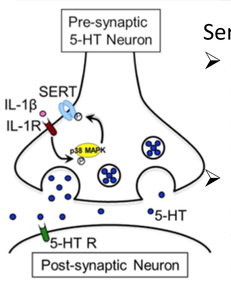
K. S. Crowson[1], D. J. Davis[2], C. E. Hagan[2]

[1]University of Missouri College of Veterinary Medicine
[2]University of Missouri Department of Pathobiology

Introduction

- Serotonin has important impacts on behavior, including: pain sensation, mood modification, sleep pattern, and aggression





Serotonin Transporter

- Allows recycling of serotonin to pre-synaptic neuron from the synaptic cleft and termination of the neural signaling
- Antidepressant and recreational drugs act to inhibit this transporter to prevent uptake and increase mood effects

- SERT KO mice are accepted as a "stress-vulnerable" mouse model, due to proposed downregulation of receptors in response to chronic persistence of serotonin in synaptic cleft

  …but when SERT KO mice were injected with LPS to induce stress, they seemed less affected by the treatment than did wild type mice.

- We decided to investigate if these stress-vulnerable SERT genotyped mice had a blunted depressive-like behavior response when induced with an exogenous stressor, LPS, compared to wild type mice as measured by locomotor activity.

Materials and Methods

Subjects:

- Twelve SERT knockout mice, broken into two treatment groups of six receiving LPS and six receiving saline.
- Twelve wild type mice, broken into two treatment groups of six receiving LPS and six receiving saline.

Treatments:

- Injections were performed with dosages of 0.005 cc/1g body weight performed parietally
  - -LPS concentration of 1 μg/ml
  - -Saline concentration of 1x

Experimental Procedure:

- SERT genotyped mice were weighed and injected with their appropriate treatment solution
- Mice were then placed in separate enclosures unexposed to other mice in view of a camera with an infrared filter
- AnyMaze software was used to track the locomotor activity of the mice within their enclosure over a 24-hour period in an isolated room to measure the amount of time spent immobile, the total distance travelled, and the number of mobile episodes

Post-Experiment Analysis:

- Mice were then euthanized, with blood serum taken and internal structures fixed with formalin during necropsy for future investigative study

Figures and Results

Figure 1

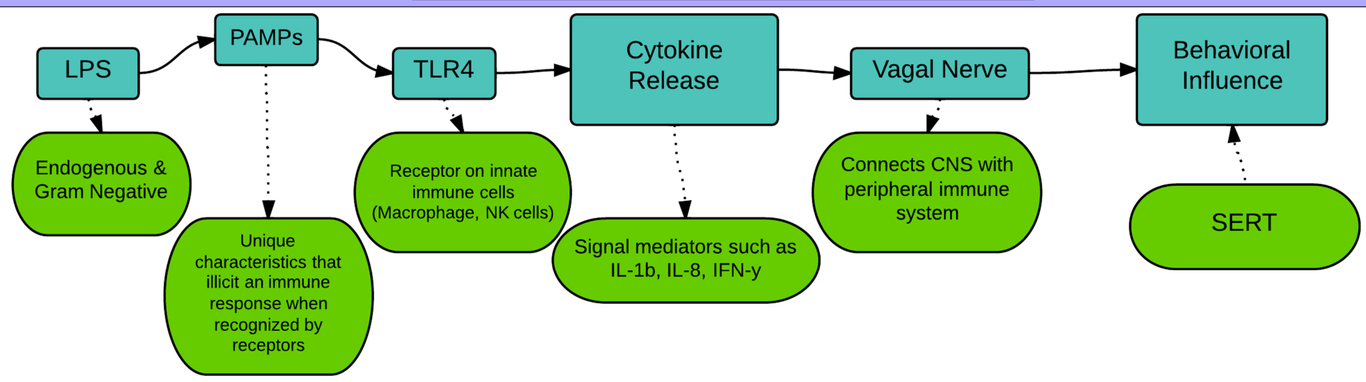


Figure 2

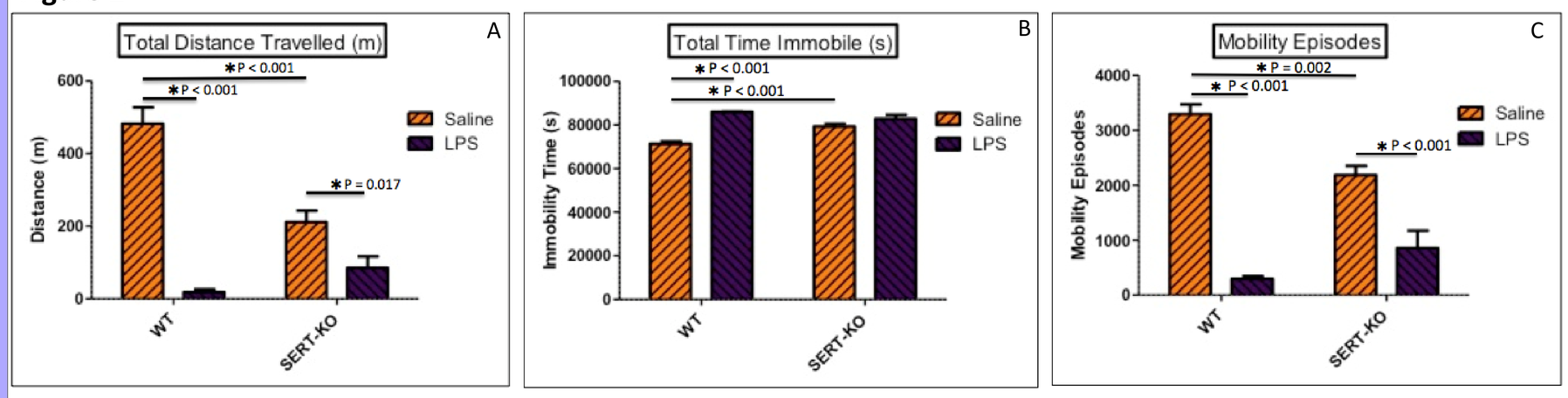


Figure 3

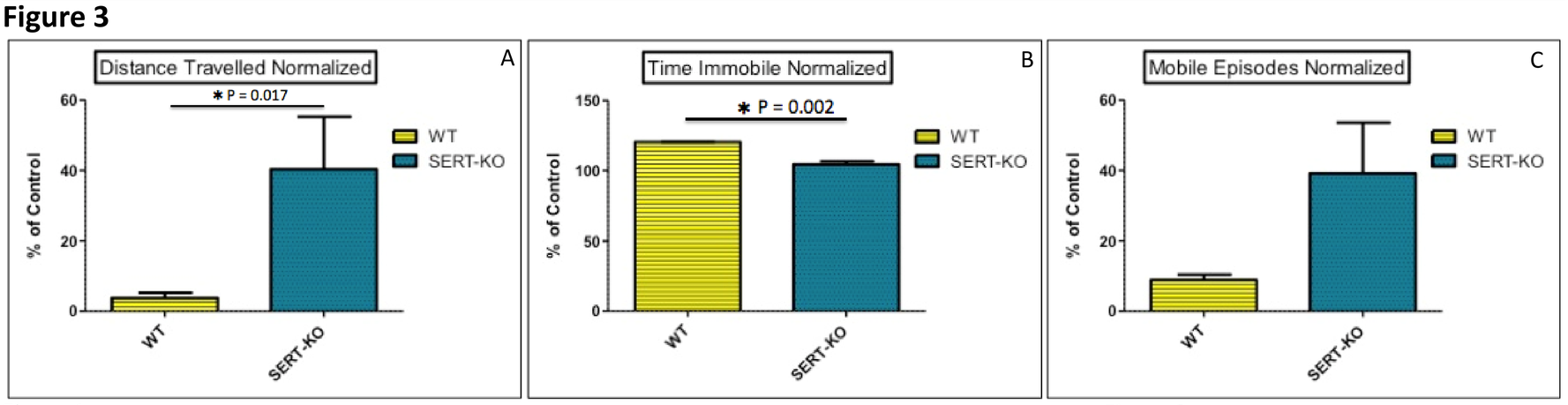


Figure 1
This linear graphical representation of the believed step-wise progression of the process of LPS inducing a depression-like state through the innate immune system

Figure 2
This series shows the total values related to locomotion calculated compared with treatment and genotype groups. **A** – The total distance travelled (m) of the study mice showed a significant difference between SERT KO and WT mice regarding saline treatment and within the respective genotypes receiving LPS/saline treatment. **B** – The total time immobile (s) showed significant difference only between the WT mice. **C** – The mobility episodes showed significant differences between SERT KO and WT mice regarding saline treatment and within the respective genotypes receiving LPS/saline treatment

Figure 4

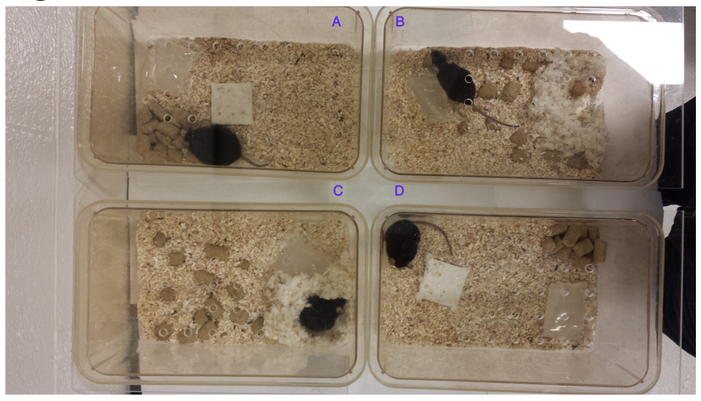


Figure 3
This series shows LPS treatment effect when normalized to the basal control levels for each respective WT or SERT KO genotype. **A** – For analysis of distance travelled, a Mann-Whitney test showed a significant difference between the genotypes. **B** – For analysis of time spent immobile, a Mann-Whitney test showed a significant difference between the genotypes. **C** – For analysis of the number of mobile episodes, a T-test was performed and the genotypes were not significantly different than one another

Figure 4
This picture displays the enclosures post 24 hour treatment of different genotypes and treatments. **A** – SERT KO treated with LPS. **B** – WT treated with saline. **C** – SERT KO treated with saline. **D** – WT treated with LPS

Conclusion

- In concordance with previous publications, we showed that the SERT KO mouse does show a greater level of depressive-like behaviors compared to WT mice by displaying significantly less distance travelled, more time spent immobile, and fewer mobility episodes when treated with saline alone

However…

- A significant difference arose between WT and SERT KO mice regarding distance travelled after treatment, with SERT KO animals moving a further total distance over 24 hours than did WT mice indicating SERT KO mice display a blunted depression-like behavioral state when injected with LPS
- A significant difference arose between WT and SERT KO mice of the total time spent immobile after LPS injections over the 24-hour period with SERT KO mice spending less time immobile, demonstrating further the blunted depression-state that the SERT KO mouse experiences compared to the WT mouse
- Overall, though the SERT KO mouse under physiologic conditions exhibits behaviors consistent with a stress-vulnerable model, when induced into a stressed state the SERT KO mouse has the predicted depression-like state blunted compared to WT mice. These findings indicate that the serotonin transporter plays an important role to behavior beyond the CNS pathway, and illuminates the need for further research of its role in the peripheral immune system

Acknowledgements

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