Proceedings of the Nutrition Society (2022), **81 (OCE1)**, E56 doi:10.1017/S0029665122000568

Winter Conference 2021, 7–8 December 2021, Obesity and the brain

Role of brain serotonin in age-related decline in physical activity in mice

P.B. Martinez de Morentin, M. Arcon, A. Leeson-Payne, Y. Martynova and L.K. Heisler
The Rowett Institute, University of Aberdeen, Aberdeen, UK

Ageing is negatively correlated with physical activity (PA) and this has an undesirable impact on overall health[1]. The neurotransmitter serotonin (5-HT) is known to be inversely correlated with physical activity[2]. Here we investigate a serotonergic neuronal circuit involved in voluntary physical activity during ageing in mice.

We injected designed DREADD proteins (Designer Receptors Exclusively Activated by Designer Drugs) that enable non-invasive control of neuronal signalling through the Gq (hMD3q, excitatory) and Gi (hMD4i) G-protein coupled signalling pathways in the dorsal raphe nucleus (DRN) of $Tph2^{iCre}$ mice (tph2, rate-limiting enzyme in 5HT synthesis) to modulate 5-HT release, or in the ventral segmental area (VTA) of $5\text{-}HT_{2C}R^{Cre}$ mice (5-HT type 2c receptor) to modulate activity in a 5-HT target region. Upon administration of CNO (clozapine-N-Oxide, Designer drug for DREADD) (1mg/kg, IP) and lorcaserin (3mg/kg, IP) we characterised the locomotor activity profile of all mice using TSE Phenomaster.

Our results showed that activation of $Tph2^{DRN}$ cells reduced PA ($p < 0.05$; Veh, $n = 11$, 12811 ± 1554 vs CNO, $n = 10$ 8196 ± 2821, $t = 2.507$,$df = 19$,) while its inhibition induced locomotion ($p < 0.001$; Veh, $n = 5$, 13209 ± 1181, vs CNO, $n = 5$, 26948 ± 2515, $t = 4.944$, $df = 8$. Chemogenetic activation of $5\text{-}HT_{2C}R^{VTA}$ reduced PA ($p < 0.05$, Veh, $n = 6$, 6650 ± 1329 vs CNO, $n = 9$, 3587 ± 401, $t = 2.606$, $df = 13$) while its inhibition reverted the effects of lorcaserin ($p < 0.01$, Lorc + veh $n = 6$, 10704 ± 1235 vs Lorc + CNO $n = 9$, 16280 ± 1405, $t = 2.930$, $df = 11$)

In summary, our data indicate that the serotonin system through the 5-HT2cR signalling in the VTA is involved in the control of locomotion and identify a means to reverse age-related decline in physical activity.

Acknowledgments

This work was supported by the BBSRC (BB/R01857X/1 and BB/N017838/1) and The Royal Society of Edinburgh (RSE1122).

References

1. Gulsvik AK *et al.* (2012) *Int J Epidemol* **41**(2), 521–530.
2. Fonseca MS, Murakami M & Mainen ZF (2015) *Curr Biol* **25**, 306–315.