A link between reduced blood oxygenation and failure in learning and memory in a mouse model of Down syndrome

Down Syndrome (DS) is the most frequent genetic cause of cognitive disability in humans, affecting more than 6 million people worldwide. Triplication of more than 300 genes on chromosome 21 results in gene dosage imbalance that affects intellectual impairments characteristic of DS. Importantly, all adults with DS will develop brain pathology similar to that of Alzheimer's disease.

While cognitive disability is a characteristic feature of DS, the molecular mechanism behind this phenotype remains obscure. Since a significant proportion of children with DS suffer from varying degrees of sleep apnea, we questioned the role of reduced blood oxygen in DS phenotype. We quantified blood oxygenation during different physiological processes in young and old Ts65Dn mice and their controls. Using the Ts65Dn mouse model of DS, we found a significant drop is blood oxygen level (i.e. hypoxemia) in these mice. Since mice are nocturnal, we predicated reduced blood oxygen during their low activity (day time) and vice versa. Surprisingly, we found increase incidence of hypoxemia during the night (high activity). Furthermore, we found that physical exercise (e.g. treadmill exercise) did not necessarily increase incidences of hypoxemia in these mice. These finding were supported by the fact that we found an increase in a gene expression for (*Cox4i2*) in the dentate gyrus of the hippocampus of the brain, i.e. an enzyme which is generally upregulated during hypoxemic incidences.

We used adolescent (2.5 months) and adult (4.5 months) male DS and age-matched normal (control) mice. Then a 24-hour oxygen saturation was recorded on a laptop, during which the mice had access to water and food.

We found that Ts65Dn mice show significant increase in the incidence of hypoxemia, as early as 10 weeks of age, while majority of hypoxemic incidences in DS mice occurred during nighttime in young adult Ts65Dn DS mice.

Similar to DS, mouse models of DS show a number of cardiac defects. However, significant physical activity in DS mice did not lead to deterioration of blood oxygen, which suggests that cardiovascular abnormalities play a minimal role in the occurrence of hypoxemia in DS mice.

Locus Coeruleus (LC) is the primary source of norepinephrine terminals for the cortex and hippocampus. These neurons induce excitatory effects on respiratory rate and inactivation of them significantly diminishes respiratory rate. Due to significant LC degeneration in DS mice, increased hypoxemic events in DS mice could be linked to LC neurons degeneration and dysfunction and vice versa.

We detected the respiratory abnormalities in DS mice at an early age of 10 weeks. This precedes the apparent cognitive dysfunctions that appear around 6 months of age in these mice. Hence, we

can postulate that the respiratory abnormalities in DS mice precipitate the innate pathological processes that lead to cognitive dysfunction in these mice.

Significance: Our data suggest that mild reduction in blood oxygen in children with DS for a lifetime could certainly be a contributing factor in cognitive dysfunction in these individuals. For this reason, routine testing of blood oxygenation in children with DS might be warranted.

Publication

Increased incidence of intermittent hypoxemia in the Ts65Dn mouse model of Down syndrome.
Das D, Medina B, Baktir MA, Mojabi FS, Fahimi A, Ponnusamy R, Salehi A
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