Impaired nitric-oxide-dependent neurovascular coupling and spatial memory in type 2 diabetes are rescued by dietary nitrate

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The coupling between neuronal activity and cerebral blood flow (CBF), known as neurovascular coupling (NVC), is essential for brain function. In the hippocampus, a region associated with memory processing and learning, NVC is dependent on nitric oxide ($^{\bullet}$NO) via the NMDAr-nNOS-SGC pathway. Consistently, limited •NO availability is linked to NVC impairment, which may lead to cognitive dysfunction as observed in several conditions, including type 2 diabetes mellitus (T2DM) (Gonçalves et al., FRBM 2022 193:669-675).

In this work we aimed to assess the functionality of NVC in connection with neuronal-derived $^{\bullet}$NO and cognitive function in an animal model of T2DM (Goto-Kakizaki – GK – rats). Further, we studied the potential of dietary nitrate (a precursor of $^{\bullet}$NO via the nitrate-nitrite-$^{\bullet}$NO pathway) to sustain the $^{\bullet}$NO-dependent NVC and thereby prevent neural and cognitive impairment. To accomplish this goal, we evaluated spatial learning and memory performance (Barnes maze, Novel Object Recognition, and Y Maze), the functionality of NVC (*in vivo* simultaneous measurements of •NO and CBF dynamics), and plasma nitrate/nitrite concentration (via gas-phase chemiluminescence) in male GK rats at 4 and 8 months of age. Age-matched Wistar rats were used as controls. Nitrate supplementation was provided in water *ad libitum* for 12 weeks.

Diabetic animals exhibited dysfunctional NVC linked to compromised $^{\bullet}$NO concentration dynamics to glutamatergic activation in correlation with impaired spatial learning and memory performance. Dietary nitrate intervention, which significantly increased the concentration of nitrate/nitrite in plasma, was able to ameliorate the NVC and spatial memory performance in GK rats, independently of glycemic control.

Our findings highlight the pivotal role of $^{\bullet}$NO in hippocampal NVC associated with spatial memory and support the potential of dietary nitrate to improve cognitive dysfunction associated with T2DM.

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