In a recent publication in The Journal of Physiology, Shoemaker et al. (2021) employed a placebo-controlled, single-blinded, randomized cross-over design assessing cognitive performance and cerebrovascular function (via TCD) pre- and post-indomethacin ingestion. Shoemaker et al. (2021) recruited 13 young (25 ± 4 years) and 12 older adults (58 ± 6 years) and hypothesized that indomethacin would impair cognition to a greater extent in older adults compared to young adults. However, in contrast to their hypothesis, and despite a 15% lower resting MCAv in the older participants, they reported cognitive resilience to an acute reduction (31%) in CBF. Remarkably, there was only a ~7% impairment in cognitive performance, in both young and older adults. This was attributed to an elevated cardiorespiratory fitness for the respective age and population of their cohort, implying that lifelong habitual activity may mitigate the cognitive impact of acutely reduced CBF. Overall, these findings provide novel data on the impact of an acute reduction of CBF in healthy ageing. These data also suggest that (i) acute reductions in CBF may not directly translate to lower cognitive performance or (ii) cardiorespiratory fitness may protect cognitive performance in the face of a CBF challenge.

The impact of sedentary behaviour on cerebral blood flow and cognition

Shoemaker et al. (2021) used indomethacin to induce an acute reversible decline in MCAv and cerebrovascular reactivity to hypercapnia (CVRCO₂) in healthy, physically active adults. A decline in MCAv has also been observed during prolonged periods of sedentary behaviour (Wheeler et al. 2019), although without any change in CVRCO₂. Ironically, it is now feasible, and indeed probable, that people achieve the recommended daily dose of physical activity at the same time as being predominantly sedentary across the day, a previously oppugnant idea that could have serious health implications. Prolonged sitting, a feature of the modern working day, negatively impacts metabolic and vascular health. It is also associated with reduced cognitive performance (Mullane et al. 2017) assessed via a similar computerized assessment to that employed by Shoemaker et al. (2021). The disparate cognitive performance reported in Mullane et al. (2017) compared to Shoemaker et al. (2021) could be mediated by the interaction between decreased CBF and altered metabolic profile, as evident in prolonged sitting, but not indomethacin ingestion.

Prolonged sitting elicits an acute decline in MCAv (~10.5%) (Wheeler et al. 2019), which is significantly lower than the magnitude of decline induced by indomethacin (~31%) (Shoemaker et al. 2021). Wheeler et al. (2019) reported that the decline in MCAv in their overweight/obese cohort was offset by either a combination of a morning bout of exercise and walking breaks throughout the day or morning exercise alone. However, exercise supplemented by walking breaks resulted in fewer sharp declines in MCAv. This implies that regular physical activity breaks promote a more temporally consistent CBF, and breaking up prolonged sitting may be important in addition to specific exercise sessions. However, the impact on cerebrovascular health remains to be determined. Furthermore, Mullane et al. (2017) reported that cognitive performance was significantly higher when undertaking hourly desk-based cycling physical activity compared to walking, standing or sitting conditions. Whether this enhanced cognitive performance could be attributed to preserved CBF is an intriguing proposition; however, previous studies by Shoemaker and colleagues do not support this notion. Sedentary behaviour results in a decline in cognitive performance (Mullane et al. 2017) and in MCAv (Wheeler et al. 2019). Despite this, a causal link between reduced CBF and impaired cognition has only been established in clinical cohorts, and not healthy individuals. Taken together, these studies suggest that meeting the physical activity guidelines alone may not be sufficient to negate the consequences of prolonged sedentary behaviour for cerebrovascular health and cognitive performance. It is especially pertinent to investigate the interaction between the age-related decline in CBF, physical inactivity and the risk of developing neuro-cognitive disease.
The influence of exercise on cerebral blood flow and cognition across the lifespan

The age-related decrease in MCAv reported in Shoemaker et al. (2021) agrees with previous reports (Bailey et al. 2013). Furthermore, the sustained cognitive performance in both young and older adults, despite a decline in MCAv following indomethacin administration, may reflect proficient cerebrovascular function as a result of chronic adherence to physical activity. Bailey et al. (2013) observed that greater aerobic fitness in young and older males is associated with an elevated resting MCAv and CVRCO₂. The similar values for aerobic capacity in healthy older adults in Shoemaker et al. (2021) and exercise-trained older males in Bailey et al. (2013) (V̇ O₂max: 42 ± 11 vs 39 ± 6 mL/min⁻¹·kg⁻¹, respectively), may reflect a lifelong, physical activity-mediated modulation of cerebrovascular regulation and CBF relative to neuronal demand. This modulation could also explain the slower decline in cognitive assessment scores in active older adults. Similarly, these physically active individuals may be at less risk of hypoxic insults and mild cognitive impairment leading to degenerative neurocognitive diseases. However, the influence of exercise training on cerebrovascular function, cerebral metabolism and cognition across the human lifespan warrants further investigation with a variety of methodological techniques. Indeed, the decline in MCAv across middle-age acquired via TCD ultrasound is not always replicated when assessing CBF via MRI (Wu et al. 2016). This may be a result of respective methodological limitations or regional anatomical and physiological cerebrovascular (mal)adaptations with age.

Wu et al. (2016) also highlight distinct alterations in CBF across childhood and adolescence, as associated with changes in cerebral structure, metabolism and cognition. Specifically, CBF increases across the evolutionary protracted stage of childhood and declines across adolescence. However, adolescence coincides with cognitive, biological, psychological and social development, alongside neural synaptic pruning and myelination, as well as cardiovascular adaptations to oxygen carrying capacity. Thus, a proportional decline in CBF across adolescence is probably not a precursor to limits in cognitive capacity.

Emerging evidence suggests that adolescence is also a key period for cerebrovascular development, where decreased resting CBF coincides with its tighter regulatory control. If adolescence represents a key anchor for developing CBF regulation, the high metabolic demands and lack of substrate storage may predispose the paediatric brain to greater cognitive risk and (mal)adaptation to recurring periods of diminished CBF, similar to that induced by Shoemaker et al. (2021). As such, optimizing CBF, metabolism and cognition during childhood is increasingly pertinent with important public health implications, as exacerbated by the effect of the COVID-19 pandemic on physical activity, sedentariness and sitting time. There is some evidence that exercise training improves facets of cognition and hippocampal blood flow in pre-adolescent children. However, the impact of exercise on cerebrovascular function, CBF, metabolism and cognitive performance throughout childhood and adolescence is equivocal. Furthermore, whether exercise training in healthy children improves indices of cerebrovascular function during relevant stimuli remains to be investigated.

Future research directions

The study by Shoemaker et al. (2021) has eloquently investigated the acute impact of indomethacin ingestion on MCAv in young and older physically active adults. Their findings provide key foundations for further research linking CBF and cognition across the lifespan. Based on the debate between TCD and MRI data, it would be intriguing to establish the global and regional CBF response to indomethacin ingestion. Furthermore, interventions specifically targeting vasoilationation or vasoconstriction of the cerebrovasculature aiming to quantify the global and regional responses across age and fitness will allow further insight into cerebral metabolism and cerebrovascular function. Longitudinal studies are required to expose the relationship between CBF and cognition across the lifespan to establish long-term implications for neurocognitive and cerebrovascular function/health. Specific attention should be paid to the role of sedentary behaviour, as well as strategies to offset this, in addition to establishing the impact of exercise training on CBF and cerebrovascular function in children.

Additional information

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