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PERSPECTIVES

Diet-induced disruption of the olfactory system: not only obesity is to blame

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Most animals have an olfactory system (OS) whose anatomy, organization and functioning are remarkably similar. The OS is responsible for the sense of smell, through which animals gather information about the chemical composition of the environment (Manzini *et al*. 2022). In most species, the sense of smell conveys essential information for finding suitable food, avoiding predators, orienting themselves in space and increasing reproductive success. This also applies to humans, where it is crucial for the enjoyment of food and strongly influences general well-being (Boesveldt & Parma, 2021). The OS also senses and responds to endogenous signals that change depending on the metabolic status. The activation of receptors expressed in cells of the OS by specific hormones and nutritional signalling molecules can influence the functioning of the OS and thus modulate the sense of smell (Fadool & Kolling, 2020).

It has long been known that obesity, that is, an excessive body fat accumulation, negatively affects our health and leads to a progressive decline of several organ systems (Tchernof & Després, 2013). More recent studies have linked obesity to cellular and molecular disruption of the OS. It has been reported that obese animals have both a smaller number of olfactory sensory neurons (OSNs) and associated projections to the olfactory bulb (OB), reduced expression of olfactory receptors, lesser amounts of olfactory G-proteins and weaker odorant-induced receptor potentials. On the level of the OB, the first relay centre of the OS, obesity alters the functioning of projection neurons, neurons that transmit olfactory information to higher olfactory centres. Together, this leads to an impaired sense of smell (Fadool & Kolling, 2020).

The apparent link between obesity and the alterations of the OS has been challenged by ground-breaking results obtained using transgenic mouse lines. While genetically obese animals that consumed a nutrient-balanced diet retained an intact OS, animals genetically resistant to obesity still exhibited a reduction of OSNs when fed a diet containing a higher amount of fat. These results led to the hypothesis that excess fat in the diet rather than obesity could trigger alterations of the OS (Fadool & Kolling, 2020).

In the current issue of *The Journal of Physiology*, Chelette and coworkers (2022) have examined this hypothesis in detail and provided compelling evidence that excess fat in the diet rather than the development of obesity is the cause for loss of OSNs and associated projections to the OB. To decouple diet-induced obesity from dietary fat consumption, the authors developed a sophisticated pair-feeding method that allowed feeding a moderately high-fat (MHF) diet while keeping the total calories the same as in a nutrient-balanced (but lower fat) control diet. Using this feeding method and a transgenic mouse line in which a specific subpopulation of OSNs can be readily visualized, the authors elegantly demonstrated the following main points:

(i) Mice (of both sexes) pair-fed an MHF diet did not become obese, but like their obese littermates (males only, see point (ii) below) having *ad libitum* access to an MHF diet and unlike littermates that received a lower-fat control diet, they lost a significant number of OSNs and associated OB projections.
(ii) Unlike their male counterparts, female mice did not develop diet-induced obesity even when they had *ad libitum* access to a MHF diet but still lost a significant number of OSNs and associated OB projections.
(iii) The loss of OSNs and associated OB projections in male mice that had *ad libitum* access to an MHF diet could not be compensated by physical activity (voluntary running).
(iv) Physically active male mice showed a loss of OSNs and associated OB projections even when they received a lower-fat control diet.

To keep things as straightforward as possible, I have focused on the results directly related to the loss of OSNs and the associated projections to the OB. However, the authors also monitored the glucose clearance ability, eating behaviour, inflammatory markers and energy metabolism in the differently fed mice. The key finding from these additional experiments is that pair feeding an MHF diet alters cytokine production and degrades the animals' ability to clear glucose. This suggests that consumption of excessive dietary fat that does not lead to obesity generally worsens the physiological health status. Also, the experiments showed that different dietary treatments could induce changes in the energy expenditure and the respiratory exchange ratio. In particular, the respiratory exchange ratio, which indicates how fuels are used by the body, decreases in the MHF pair-fed male mice during the light cycle, so that a greater percentage of fats are used as fuel rather than carbohydrates. This could prevent overt obesity while not mitigating inflammation or loss of OSNs and the associated projections to the OB.

Together, the results obtained by Chelette and coworkers provide direct evidence that a diet-induced loss of cellular components of the OS and a general impairment of the health status is not necessarily related to the development of obesity but is instead connected to the excessive consumption of dietary fat. Importantly, they showed that this is true for males and females. While this is crucial to understanding the relationships between diet, the OS and overall health, several important questions remain open. Does a high-fat diet affect multiple subpopulations of OSNs, or is the effect limited to one or a few OSN subpopulations that may be associated with specific odours? How do

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these cellular changes of the OS affect olfactory perception and performance? By which signalling pathways and molecular mechanisms do fatty diets change the OS? Do fatty diets similarly affect the human OS? Answering these questions would presumably allow a better understanding of the impact of a fatty diet on the OS and overall health.

Together, the results obtained by Chelette and coworkers are significant findings that will most likely have important implications for the entire field of nutritional physiology.

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Additional information

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Supporting information

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