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The non-neuronal cholinergic system in the inflamed adipose tissue of obese mice

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A key feature of morbid obesity is white adipose tissue (WAT) inflammation. In obese animals and humans WAT is infiltrated by macrophages that are mainly found at sites where adipocytes die by pyroptosis [1]. Here, macrophages sequester and digest adipocyte debris, forming distinctive crown-like structures [2]. Acetylcholine (ACh) was the first neurotransmitter to be discovered. However, within the past decades increasing experimental evidence has shown that ACh is also produced by non-neuronal cells and tissues, including the immune cells, where it acts as a secreted messenger. Here we evaluated whether the non-neuronal cholinergic system occurs in obese and inflamed fat. By RT-qPCR, we found that all the components of the non-neuronal cholinergic system molecular machinery significantly increased in subcutaneous and visceral WAT from high-fat diet obese mice compared with mice fed a normal diet. By immunohistochemistry and confocal microscopy, we found that about 40-50% of macrophages infiltrating obese WAT expressed choline acetyltransferase (ChAT), choline transporter-1 (ChT-1) and the vesicular ACh transporter (VAChT), whereas the white adipocytes expressed the butyrylcholinesterase (BChE). In vitro studies showed that white adipocytes differentiated from human multipotent adipose-derived stem cells not only produced BChE but also, and to a larger amount, acetylcholinesterase (AChE). Collectively, these data suggest that a consistent proportion of macrophages infiltrating obese WAT produce and secrete ACh that may act on ACh receptor-bearing adipocytes; diffusion of this potent molecule is prevented by ACh re-uptake by macrophages (through VAChT) or by adipocyte degradation of ACh (through BChE and AChE) into acetate and choline, which is quickly taken up by the macrophages (through ChT-1). Promoting the anti-inflammatory effect [3] of the non-neuronal cholinergic system present in obese fat could represent a novel and effective therapeutic approach to obesity and associated diseases.

References

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Key words

Acetylcholine, inflammation, macrophages, obesity.