Ruprecht-Karls-Universität Heidelberg
Medizinische Fakultät Mannheim
Dissertations-Kurzfassung

Accumulation of omega-6 derived trans, trans-2,4-decadienal promotes microvascular disease by disrupted insulin signaling

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Essential fatty acids, including both omega-3 and omega-6, are vital nutrients that can only be obtained from our diets. These fatty acids are crucial for health, with an ideal dietary ratio of omega-6 to omega-3 falling between 1:1 and 2:1 to prevent chronic illnesses. Unfortunately, modern dietary patterns, particularly in Western diets, have distorted this ratio to an unhealthy level of 15:1 to 16.7:1, mainly due to an overconsumption of linoleic acid, which constitutes over 90% of our polyunsaturated fatty acid intake. A significant surge of 1000-fold in vegetable oil consumption, primarily abundant in omega-6 fatty acids, has coincided with a substantial 12-fold increase in diagnosed diabetes prevalence and a 3-fold rise in obesity rates in the United States, while the implications of high omega-6 fatty acid intake for diabetic patients remain a subject of debate. Increased consumption of omega-6 PUFAs, especially when exposed to oxidative conditions like heating, leads to the formation of highly reactive carbonyl species (RCS), mainly trans, trans-2,4-decadienal (tt-DDE). Comparable to other RCSs like 4-hydroxynonenal (4-HNE), acrolein (ACR), acetaldehyde, and methylglyoxal (MG), the timely and efficient detoxification of tt-DDE is essential in order to prevent harm and associated diseases.

In this study, we identified the enzyme Aldh9a1b as having a key role in the detoxification of tt-DDE. Loss of Aldh9a1b increased tt-DDE levels and resulted in an abnormal retinal vasculature and glucose intolerance in *aldh9a1b*$^{-/-}$ zebrafish. Transcriptomic and metabolomic analyses revealed that tt-DDE and *aldh9a1b* deficiency in larval and adult zebrafish induced insulin resistance and impaired glucose homeostasis. Moreover, alterations in hyaloid vasculature induced by *aldh9a1b* knockout or by tt-DDE treatment could be rescued by the insulin receptor sensitizers metformin and rosiglitazone. Collectively, these results demonstrated tt-DDE is the substrate of Aldh9a1b which causes microvascular damage and impaired glucose metabolism through insulin resistance.

In conclusion, the zebrafish model has been shown to be useful to provide a previously unexpected explanation for the microvascular disorders seen in patients with prediabetes. Our research point to an important role of Aldh9a1b for controlling omega-6-derived reactive RCS, especially tt-DDE, which will if not sufficiently detoxified, trigger a cascade from insulin resistance, increased gluconeogenesis and altered fatty acid metabolism, consequently leading to microvascular disease.