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Glycine contributes to the control of hepatic response to insulin by promoting mitochondrial-endoplasmic reticulum interactions

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Abstract

Introduction

Determinants of health and diseases in humans involve complex interactions between diet, gut microbiota and host metabolism. The liver is a major organ that coordinates host adaptations to environmental factors. Mitochondria and endoplasmic reticulum tightly regulate liver nutrient sensing and metabolic adaptations, shaping its metabolic flexibility. Both organelles interact through contact points (named MAMs) in order to exchange calcium and lipids, and MAMs' integrity settles metabolic flexibility of the liver. Disrupted MAMs' integrity in obesity is linked to liver steatosis and insulin resistance. This occurs in association with alterations circulating amino acid profiles, among which glycine. Meta-analyses showed that the low plasma glycine concentration observed in obesity is a predictive factor for developing type 2 diabetes. We thus aimed at exploring whether glycine could participate to the regulation of the hepatic response to insulin and whether mechanisms may involve regulation of mitochondrial-ER (MAMs) interactions.

Materials and Methods

The study was carried out in 12 week-old male C57B16J mice fed a standard chow (n = 12/group, 36 total) in accordance with the French guidelines for the care and use of animals. Glycine (1.2g/kg) was provided for 3 days in drinking water vs. water vs. isonitrogenous placebo amino acids. Liver was collected after an overnight fast, 15 min after ip injection of saline (n = 6/group) or insulin (0.75U/kg, n = 6/group). Liver samples were fixed in glutaraldehyde/cacodylate for quantifying MAMs by transmission electronic microscopy. Fractions enriched in MAMs were isolated by differential ultracentrifugation on fresh tissue for Western Blot explorations. Insulin response was assessed through Akt phosphorylation at Ser473.

Results

Glycine supplementation increased the percentage of interaction between ER and mitochondria (compare to mitochondrial surface) for all spacing from 10 to 50 nm. Thus, glycine supplementation induced a 45% increase in mitochondrial-ER (MAMs) interactions compared to other groups ($p < 0.001$). In agreement to the improved MAMs' integrity, insulin response was enhanced by 50% after glycine supplementation compared to other groups ($p < 0.05$). Finally, protein analysis of the MAMs' fraction corroborates the importance of PP2A as a key enzyme regulating MAMs' integrity.

Conclusion

Glycine is therefore an interesting nutritional actor that can play a crucial role in regulating the integrity of MAMs in the liver, thus contributing to the control of the insulin response.

Conflict of Interest

There is no conflict of interest