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Serine supplementation alleviates neuropathy in diabetic mice

Aim: This study aimed to investigate how altered serine metabolism can represent a contributing factor to diabetes-associated peripheral neuropathy in mouse models.
Methods: To determine whether long-term, chronic serine deficiency drives peripheral neuropathy, the authors fed mice either control or serine-free diets in combination with either low-fat or high-fat diets for up to 12 months. The mice were then tested for small sensory fiber degeneration by thermal latency quantifications and Intraepidermal nerve fiber density analyses. In serine-deficient conditions, serine palmitoyl transferase (SPT) (an enzyme important in the biosynthesis of sphingolipids) incorporates other amino acids including alanine, to form non-canonical deoxysphingolipids. To assess the contribution of these atypical lipid species to the progression of serine-related peripheral neuropathy, the researchers tested the compound myriocin, an inhibitor of the SPT enzyme, in mice fed the diet described above for 6 months and then quantified sphingolipid diversity and thermal sensing. Finally, to investigate the protective role of serine supplementation, the authors fed db/db mice a diet enriched with 3% serine from 6 weeks of age and quantified the neuropathy phenotype.
Results: The researchers showed that low serine, in combination with a high-fat diet, accelerated the onset of peripheral neuropathy in the mice. Myriocin treatment attenuated symptoms of peripheral neuropathy in mice fed a serine-free high-fat diet. Similarly, in diabetic db/db mice, serine supplementation slowed the progression of peripheral neuropathy and the mice recovered.
Conclusions: These results indicate that systemic serine deficiency and dyslipidemia represent a new therapeutically exploitable risk factors for peripheral neuropathy.

Comments. Neuropathy is a common complication of diabetes, with very limited effective therapeutic interventions. With this current preclinical study, the authors from the Salk institute elegantly demonstrate a relationship between neuropathy and altered serine metabolism in mice. Over the years, serine deficiency has been implicated in a variety of neurodegenerative diseases, including modulating macular disease and peripheral neuropathy. The authors of this study found that diabetic mice with low levels of two related amino acids, serine and glycine, had an increased risk for peripheral neuropathy. They also found that either normalizing plasma serine levels through dietary supplementation or mitigating dyslipidemia with myriocin reduced neuropathy in diabetic mice. This establishes a strong link between serine-associated peripheral neuropathy and sphingolipid metabolism. However, several questions remain open, such as: What are the mechanisms of toxicity of altered sphingolipids in the nerves, and which cells of the nerve are affected? What is the impact of serine deprivation and supplementation on the total lipid profile of nerve tissues? And as this paper broadly dealt with only non-painful neuropathic models, what would be the effect of serine deficiency in a model of painful diabetic neuropathy? More work needs to be done on mice before we extrapolate these results in human settings. Nonetheless, the findings of this publication add to growing evidence that certain "non-essential" amino acids (NEAAs) play important roles in the nervous system and provide a potential new method for identifying people at high risk of peripheral neuropathy, as well as a possible treatment option.

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Reference. Handzlik MK, Gengatharan JM, Frizzi KE, McGregor GH, Martino C, Rahman G, Gonzalez A, Moreno AM, Green CR, Guernsey LS, Lin T, Tseng P, Ideguchi Y, Fallon RJ, Chaix A, Panda S, Mali P, Wallace M, Knight R, Gantner ML, Calcutt NA, Metallo CM. Insulin-regulated serine and lipid metabolism drive peripheral neuropathy. Nature. 2023 Feb;614(7946):118-124. doi: 10.1038/s41586-022-05637-6. Epub 2023 Jan 25. PMID: 36697822
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