Blocking the Lipid Metabolism as a New Treatment Strategy for Multiple Sclerosis

Anne Skottorp Mørkhoit, Agnete Larsen, Jette G. K. Nieland, Shohreh Issazadeh, Søren Nielsen and John Dirk Nieland

1Laboratory of Metabolism Modifying Medicine, Department of Health Science and Technology, Aalborg University, Denmark
2Department of Biomedicine, Aarhus University, Denmark
3Meta-IQ ApS, Aarhus, Denmark
4Biotech Research & Innovation Centre, Copenhagen University, Denmark
Correspondence: jdr@hst.aau.dk

Abstract

Multiple Sclerosis is a complex disease, which has been regarded as both a neurodegenerative and inflammatory disease characterized by damage to myelin sheaths of neurons. Normally, lipids of the CNS are important for a lot of functions e.g. hiding the myelin sheath proteins for the immune system and structure of myelin sheaths. Disturbances in metabolic pathways, as seen in Multiple Sclerosis, result in the breakdown of myelin sheaths, thus changing the composition and level of lipids compared to healthy individuals. By blocking Carnitine Palmitoyl Transferase-1A (CPT-1A), a key molecule involved in lipid catabolism, the metabolism is reversed to glucose metabolism. This block of lipid metabolism causes reparation of myelin sheaths, re-secretion of myelin sheath proteins thereby shielding these for the immune system and finally, restoration of signaling capacity of receptors using lipids. People carrying CPT-1A mutations are protected against developing Multiple Sclerosis and other CNS diseases. These mutations reduce or delete the activity of CPT-1A. The Hutterite and Inuit populations are carrying CPT-1A mutations and the prevalence of developing Multiple Sclerosis is 1/1100 and 1/5000, respectively. Normally, the prevalence in these regions is 1/350. Experimental Autoimmune Encephalomyelitis (EAE) models in rats and mice were established in order to test the effect of Etomoxir, a CPT-1A antagonist. The mice EAE model shows 50 % healthy mice after two weeks of treatment with Etomoxir. In addition, the inflammatory response is downregulated and the myelin sheaths are functional. The EAE model shows 25 % disease free animals after treatment with Etomoxir started at day 7. Blocking the lipid catabolism through inhibition of CPT-1 opens new avenues for the treatment of Multiple Sclerosis and stands for a paradigm shift in the understanding of the development and treatment of Multiple Sclerosis and other CNS diseases.

Methods

Experimental Autoimmune Encephalomyelitis Mice Model
12 weeks old female C57BL/6 mice with an average weight of 23.5 g were injected intradermal with Myelin Oligodendrocyte Glycoprotein (MOG35-55) conjugated with Freund’s adjuvant. The mice were weighted and scored daily. At day 10 after disease induction, the mice were treated with Etomoxir (MOG-001) and compared to a placebo group (Figure 3).

Experimental Autoimmune Encephalomyelitis Rat Model
2 months old female Lewis rats with an average weight of 200 g were injected intradermal with MOG35-55 conjugated with Freund’s adjuvant. The rats were weighted and scored daily. In the first study, rats were treated with Etomoxir at day 7 and compared to a placebo group (not illustrated). In the second study, rats were treated at day 1 or day 5 with either Etomoxir or Interferon-β (Figure 4).

Conclusions

• Treatment with Etomoxir ameliorates characteristic symptoms of Multiple Sclerosis investigated by the well-established EAE model of Multiple Sclerosis.
• Treatment with Etomoxir restores neuronal function in 50 % of mice (day 24) and 25 % of rats (day 7).
• CPT-1 is a key molecule involved in lipid metabolism and people with a CPT-1A mutation are protected from developing all types of Multiple Sclerosis.

Perspectives

• Generation of Inuit mice with a CPT-1A mutation.
• Immunohistochemistry for CPT-1A and myelin basic protein from sections of Multiple Sclerosis patients.
• Etomoxir is ready for clinical phase II trials in secondary progressive Multiple Sclerosis and acute optic neuritis.

RESULTS

Elomoxir Blocks Lipid Metabolism in a mice EAE model of Multiple Sclerosis

Elomoxir decreases Deteriorates Scores in a rat EAE model of Multiple Sclerosis

Figure 5: Mean disease score of day 10 to 24 after disease induction in mice receiving either Etomoxir or placebo. The statistical analysis applied is a two-way repeated measured ANOVA test. Results are presented as mean ± SEM. There is no significant difference in mean disease score between the groups (p=0.2987).

Figure 6: Percentage of healthy animals (corresponding to a score 0) at day 24 and a sum disease score of group 7 after two weeks of treatment with either Etomoxir or placebo. The statistical analysis applied is a significant difference between disease treatment with Etomoxir (n=27) and placebo (n=27). p=0.0342

Figure 7: Mean disease score of day 7 to 11 after disease induction in rats receiving either Etomoxir or placebo. The statistical analysis applied is a two-way repeated measured ANOVA test. Results are presented as mean ± SEM. There is no significant difference in mean disease score between the groups (p=0.1562) and placebo (n=20) at day 11. p=0.0013

Elomoxir improves action in mice model of Multiple Sclerosis

Elomoxir improves action in a rat model of Multiple Sclerosis

Figure 10: Mean disease score of day 7 to 11 after disease induction in rats treated with either Elomoxir or placebo. The statistical analysis applied is a two-way repeated measured ANOVA test. Results are presented as mean ± SEM. At day 10 and 11, statistical significant differences between treatment with Etomoxir (day 10 and 5) and placebo (day 1 and 5) are found.

Figure 11: Percentage rate of the five treatment groups distributed over disease score 0, 3 and disease score 4 or 5 at day 11 after disease induction (n=13 in each group).

Humane Data

Table 1: Overview of CPT-1A mutations in the Canadian people, Hutterites, and Inuits.