Identifying the Role of Lipid Metabolism in Central Nervous Systems Diseases; Is There a Common Theme for MS, ALS, Parkinson's Disease and Depression?

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Abstract

Background: Multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), Parkinson's Disease (PD) and depression, have a number of common pathogenic and metabolic mechanisms, which includes 1) an inflammatory component, 2) stress as a critical factor, 3) upregulated lipid metabolism, 4) high prevalence of depression. Further, humans with inherited specific *carnitine palmitoyl transferase 1a* (CPT1a) gene mutations have a reduced lipid metabolism and are protected from MS and depression. One key aspect in all above mentioned diseases is dysregulation of metabolism in general and alteration of lipid metabolism in particular. Studies indicate that blocking CPT1 by etomoxir and hence reversing metabolism from fatty acids to glucose is effective as treatment in animal models of MS and depression. The aim of this study was to clarify the role of CPT1 in a transgenic *sod1* G93A mouse model of ALS and a toxic rotenone PD mouse model and compare this role with the effects seen in EAE and depressions animal model.

Methods:

B6.Cg-Tg(SOD1*G93A)1Gur/J mice was bought from Jackson Laboratories and maintained by mating B6.Cg-Tg(SOD1*G93A)1Gur/J male mice to female C57Bl/6J mice. Mice were weighted three times a week from day 40 (week 1) and neurologically scored once a week from day 43. From day 55 motor function was assessed weekly by hangwire and rotarod test. Etomoxir and placebo treatment began at day 100. Treatment continued until the animals reached week 16. C57Bl/6 mice received 30mg/kg Rotenone or 0.5% carboxyl methylcellulose (CMC) oral for 32 days to induce PD. After day 32 mice were treated with etomoxir or placebo until day 61 alternating with rotenone or 0.5% CMC every other day except from day 50 until day 56 and day 58 to day 60 were mice received Etomoxir or placebo daily. During the experiment mice were evaluated by different motor and sensorimotor tests. The experiment was terminated at day 62.

Results: Transgene mice treated with etomoxir and mice induced with rotenone PD symptoms showed significant differences compared to sick mice treated with placebo.

Conclusions:

Our findings indicated that CPT1 is a key molecule involved in lipid metabolism and that inhibition of CPT1 by etomoxir potentially could be effective in animal models ALS and PD. This is consistent with our earlier findings in animal models of MS and depression.

Background

Neurodegenerative diseases like multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), Parkinson's Disease (PD) and depression, have a number of common pathogenic and metabolic mechanisms, which includes 1) an inflammatory component, 2) stress as a critical factor, 3) upregulated lipid metabolism, 4) high prevalence of depression. Further, humans with inherited specific *carnitine palmitoyl transferase 1a* (CPT1a) gene mutations have a reduced lipid metabolism and are protected from MS and depression. One key aspect in all above mentioned diseases is dysregulation of metabolism in general and alteration of lipid metabolism in particular. Studies indicate that blocking CPT1 by etomoxir and hence reversing metabolism from fatty acids to glucose is effective as treatment in animal models of MS (Figure 1) and depression (1). Further, studies indicate connections between upregulation of CPT1, inflammation and production of reactive oxygen species (2,3). The aim of this study was to clarify the role of CPT1 in a transgenic *sod1* G93A mouse model of ALS and a toxic rotenone PD mouse model and compare this role with the effects seen in EAE and depressions animal model

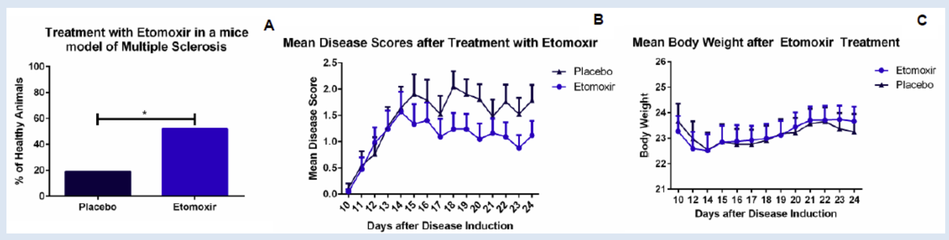

Figure 1: Two weeks of treatment with etomoxir 1 mg/kg/day subcutaneous compared to placebo treatment of mice with MOG-peptide induced EAE.

A) At Day 25 52% of the Etomoxir treated animals are symptom free determined as clinical score 0 (p=0.009 compared to placebo).

B) 3 days after start of etomoxir treatment clinical efficacy is statistically significantly improved as compared with placebo treated animals (p< 0.05).

C) Time-course of body weight changes in response to etomoxir or placebo treatment of mice with EAE. The average body weight was significantly higher in the mice subjected to etomoxir treatment as compared to placebo treated animals (at Day 25: p<0.01)

(1): Skøttrup et al (2017) Sci Rep *7*, 1–9 .
(2): Shriver et al (2011) *Sci Rep*, *1*, 79.
(3): Van der Windt et al (2012) *Immunity*, *36*(1), 68–78.

Conclusions

Studies have indicated that blocking CPT1 in animal models of MS and depression is effective. Data presented in this poster indicate that blocking CPT1 in animal models of ALS and Parkinson's disease could be effective. Studies indicate that blocking CPT1 potentially could be effective by reducing inflammation, production of reactive oxygen species and restoration of glucose metabolism. However, further studies are required.

Acknowledgements

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Methods

Transgenic SOD1 mice study:

B6.Cg-Tg(SOD1*G93A)1Gur/J mice was bought from Jackson Laboratories and maintained by mating B6.Cg-Tg(SOD1*G93A)1Gur/J male mice to female C57Bl/6J mice. Transgenic female mice (Tg Female) and their wildtype littermates (WT) were weighted three times a week from day 40 (week 1) and neurologically scored once a week from day 43. From day 55 motor function was assessed weekly by hangwire and rotarod test (week 3). Etomoxir and placebo treatment began at day 100. Treatment continued until week 16.

Rotenone mice study:

C57Bl/6 mice received Rotenone (30mg/kg) or CMC (0.5%) by oral gavage for 32 days to induce PD. After day 32 mice were treated with etomoxir or placebo every other day alternating with rotenone or 0.5% CMC until day 49. From day 50 until day 56 mice received Etomoxir or placebo daily. At day 57 mice received rotenone or 0.5% CMC and from day 58 until day 60 mice received Etomoxir or placebo. During the experiment mice were evaluated by different motor and sensorimotor tests. Final tests were done at day 54 and day 60.

Results

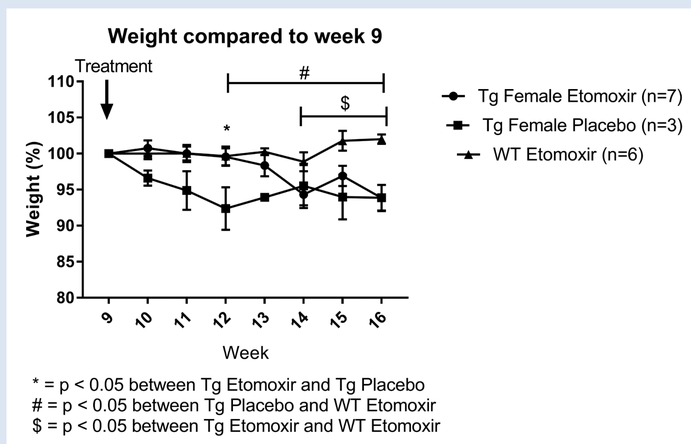

Figure 2: Weight in percent compared to weight at week 9 before treatment start. Transgenic mice treated with etomoxir presented with a general slower weight loss. Weight differences was significant different at week 12. Statistics: RM Two way ANOVA with Tukey.

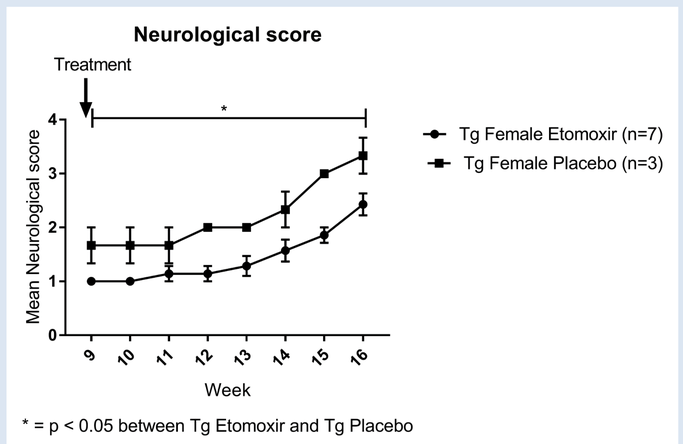

Figure 3: Neurological score was assessed weekly. Mice treated with etomoxir had a significant lower mean neurological score compared to placebo mice throughout the treatment period. Statistics: RM Two way ANOVA with Tukey.

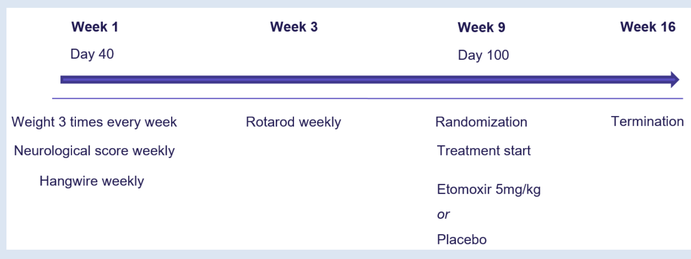

Figure 4: The experimental setup for the transgenic *sod1* G93A study

Neurological score	Function
1	Tremor in hindlims
2	No full extension of hindlimbs
3	Difficult walking / wobbling
4	Dragging of one / both hindlimbs
5	Animal not able to wright itself within 30 seconds

Table 1: Neurological score system for the SOD1 G93A mice

Results

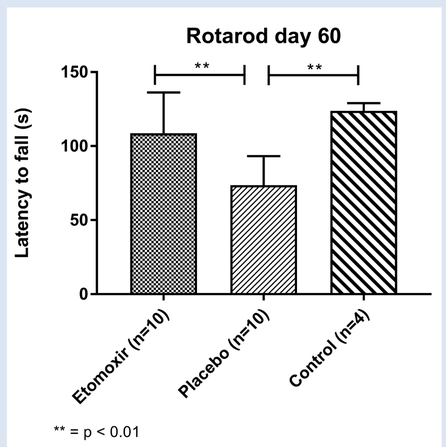

Figure 5: PD induced C57Bl/6 mice treated with etomoxir had a significant higher latency to fall compared to PD induced mice treated with placebo. Furthermore, mice treated with placebo had a significant lower latency to fall compared to control mice receiving vehicle. Statistics: One way ANOVA with Tukey.

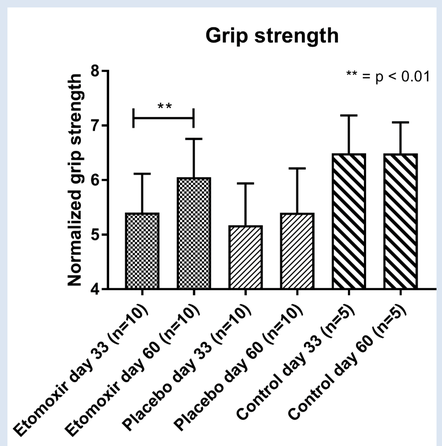

Figure 6: PD induced C57Bl/6 mice treated with etomoxir had a significant higher grip strength compared to day 33 where mice were mice presented with PD symptoms. PD induced mice receiving placebo did not improve significantly compared to day 33. Control mice did not show any change in grip strength. Statistics: Paired t-test.

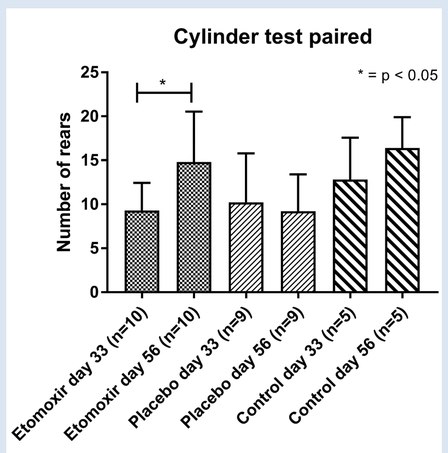

Figure 7: PD induced C57Bl/6 mice treated with etomoxir had a significant higher grip strength compared to day 33 where mice were mice presented with PD symptoms. PD induced mice receiving placebo did not improve significantly compared to day 33. Control mice did not show any change in grip strength at day 60. Statistics: Paired t-test.

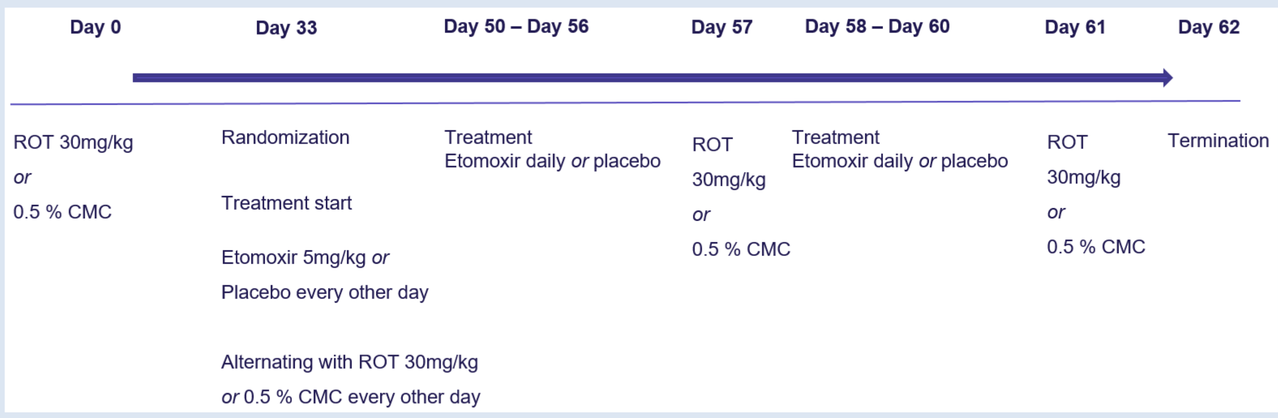

Figure 8: The experimental setup for the toxic rotenone mouse model