

# **NNPDF-Funded Research Grant # 35**

**TITLE: SSRIs as a potential therapy for NP-C**  
**PROJECT INVESTIGATOR: Synthia Mellon, Ph.D.**

**PERIOD: 4/1/2004 - 3/31/2005**

## **PROJECT DESCRIPTION**

Neurosteroids affect growth, differentiation, and survival of neurons and glia in the brain. We showed that the ability of brains from NP-C mice to produce the neurosteroid allopregnanolone (ALLO) was substantially reduced even before neurologic problems were visible. Treatment of NP-C mice with ALLO resulted in increased longevity, delayed onset of tremor, incoordination and motor loss, and delayed weight loss. ALLO treatment also resulted in increased cerebellar neuronal survival at 63 days. ALLO has not yet been approved for use in human beings. Therefore, if we could find a clinically approved drug that could increase ALLO production, it might be a useful substitute for ALLO, and might be effective for treatment of NP-C in human beings. Work from other laboratories as well as from our own demonstrated that drugs used to treat behavioral disorders in human beings, selective serotonin reuptake inhibitors (SSRIs) such as Prozac, can increase ALLO production in the brain. Therefore, we wish to determine 1.) whether other SSRIs, in addition to Prozac, will increase ALLO production in normal mice, and 2.) whether these SSRIs will also increase ALLO production in the brains of NP-C mice. Successful outcomes from these experiments will provide evidence that SSRIs can be effective in changing allopregnanolone concentrations in both wild type mice and in NP-C mice, and will provide the rationale for performing future treatment trials in NPC mice.

## **FINAL STATUS REPORT**

**Dated 2/3/2006**

Research from our laboratory previously demonstrated that a new class of compounds, called neurosteroids, may be useful in treating NP-C. Neurosteroids are compounds that are synthesized in the brain and affect neuronal growth and differentiation. We showed that NP-C mice are less able than normal mice to synthesize the neurosteroid allopregnanolone. When we treat NP-C mice with allopregnanolone, they live about twice as long, and have significant delays in neurological impairment. In addition, the allopregnanolone treatment rescues cerebellar Purkinje neurons from degeneration. While it would be ideal to test the effectiveness of allopregnanolone in children with NP-C, allopregnanolone has never been used as a drug in people, and it is not approved by the FDA for use in people for any purpose. Therefore, we wanted to find another medicine that is already approved, that could increase allopregnanolone production. We reasoned that selective serotonin reuptake inhibitors (SSRIs) that are used to treat diseases such as depression might be good candidates.

Research from several laboratories previously showed that one SSRI, fluoxetine (Prozac) could increase allopregnanolone concentrations in rats and in people with clinical depression. Therefore, we

hypothesized that Prozac might also increase allopregnanolone production in normal or in NP-C mice. We further hypothesized that as a consequence of fluoxetine treatment, NP-C mice would live longer and would have delayed neurological decline.

We tested these hypotheses in normal and in NP-C mice. We treated NP-C mice with fluoxetine at 14 days of age, and once a week for the rest of their lives. We found that fluoxetine treatment had no effect on the lifespan of the NP-C mice. Treated and untreated NP-C mice both lived to about 10 weeks of age. We also determined if neurological deficits were delayed in the mice treated with fluoxetine. We found that fluoxetine-treated and untreated NP-C mice both began tremors at roughly the same age (~52 days), and ataxia was seen at ~56 days in both groups of animals. There was also no difference in the way the mice gained and lost weight over the course of their lifetime, or in their motor coordination and locomotion. Therefore we conclude that fluoxetine treatment is not effective at increasing lifespan or delaying the neurological symptoms in NP-C mice.

**PUBLICATIONS:**

<http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pmcentrez&artid=2323675>

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