NNPDF-Funded Research Grant # 34

TITLE: NMDA receptor hypofunction in Niemann-Pick disease Type A
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PERIOD: 3/1/2004 - 2/28/2005

PROJECT DESCRIPTION

Our idea all started when we made the observation that the pattern of neurodegenerative events in the brains of Niemann-Pick Type A ("NPA") disease patients had some striking similarities to two other known disease syndromes, namely the fetal alcohol syndrome (FAS) and the intoxication with anesthetics (IWA). These syndromes are caused by the chemical suppression of the activity of a very important brain protein (the NMDA receptor), which is in part responsible for the communication between nerve cells, and thus for many learning, memory, perception and movement processes. We wondered whether some endogenous chemical compound might accumulate in the brains of NPA disease patients that might have a similar suppressive effect on NMDA receptors, and we have identified in preliminary experiments one candidate chemical compound having this activity.

What we would like do with the support of the National Niemann-Pick Disease Foundation is the following:
(i) To characterize how this compound suppresses NMDA activity, and
(ii) to test in animal models of NPA disease whether the activity of NMDA receptors really is inappropriately suppressed during the course of the disease.
The main focus of our laboratory is the NMDA receptor, so all the experimental settings and necessary expertise are readily available.

If our preliminary data are confirmed, our results would have a direct impact on the development of investigational drugs for NPA disease, since other drugs have had a beneficial effect on the aforementioned "sister diseases" (FAS and IWA). These drugs might then be immediately tested in animal models of NPA disease and eventually in humans.

FINAL STATUS REPORT
Dated 2/28/2005

In Niemann-Pick Disease of Type A, a severe developmental disorder of the brain is induced by an inherited loss of function of the enzyme acidic sphingomyelinase, which is responsible for the degradation of the brain structural compound sphingomyelin. As a consequence, sphingomyelin accumulates and causes a large number of other lipids to accumulate in succession. Despite intensive research, all attempts to identify the main toxic ingredient among these lipids have been unsuccessful.

With the support of the National Niemann-Pick Disease Foundation, we have had the opportunity to

sleuth a so far enigmatic molecule, sphingosylphosphorylcholine (SPC), which enormously accumulates in the affected children's brains. SPC is a direct metabolic descendant of sphingomyelin, and - as we now know - exerts a specific neurotoxic effect in neurons: It blocks the major structure which is responsible for the maturation of the brain as well as for most learning processes and the establishing of memory, the NMDA receptor.

What we have done with the National Niemann-Pick Disease Foundation's help is to characterize the toxicity of SPC in immature brain cells, to study the molecular interaction of SPC on NMDA receptors in detail, and to investigate the toxic effects of SPC in the developing brain in model animals. The results indicate that SPC is a plausible candidate for the main neurotoxic effector lipid in Niemann-Pick Disease Type A. Our results have prepared the basis for devising therapeutic treatment experiments in animals, whose long-term results might finally prove the blame of SPC as the ultimate toxin in this devastating disease.

PUBLICATIONS:
No Publications on this Work To Date