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Research Report

Alterations in striatal dopamine catabolism precede loss of substantia nigra neurons in a mouse model of juvenile neuronal ceroid lipofuscinosis

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ABSTRACT

Batten disease, or juvenile neuronal ceroid lipofuscinosis (JNCL), results from mutations in the *CLN3* gene. This disorder presents clinically around the age of 5 years with visual deficits progressing to include seizures, cognitive impairment, motor deterioration, hallucinations, and premature death by the third to fourth decade of life. The motor deficits include coordination and gait abnormalities, myoclonic jerks, inability to initiate movements, and spasticity. Previous work from our laboratory has identified an early reduction in catechol-O-methyltransferase (COMT), an enzyme responsible for the efficient degradation of dopamine. Alterations in the kinetics of dopamine metabolism could cause the accumulation of undegraded or unsequestered dopamine leading to the formation of toxic dopamine intermediates. We report an imbalance in the catabolism of dopamine in 3 month $Cln3^{-/-}$ mice persisting through 9 months of age that may be causal to oxidative damage within the striatum at 9 months of age. Combined with the previously reported inflammatory changes and loss of post-synaptic D1α receptors, this could facilitate cell loss in striatal projection regions and underlie a general locomotion deficit that becomes apparent at 12 months of age in $Cln3^{-/-}$ mice. This study provides evidence for early changes in the kinetics of COMT in the $Cln3^{-/-}$ mouse striatum, affecting the turnover of dopamine, likely leading to neuron loss and motor deficits. These data provide novel insights into the basis of motor deficits in JNCL and how alterations in dopamine catabolism may result in oxidative damage and localized neuronal loss in this disorder.

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1. Introduction

Juvenile neuronal ceroid lipofuscinosis (JNCL) is an autosomal recessive neurodegenerative disorder with an average age of onset around 5 years with patients typically not surviving past their third decade of life. This disease, resulting from a mutation in the *CLN3* gene, manifests with visual deficits but progresses to include seizures, motor problems, cognitive impairment, and, in some cases, hallucinations and schizophrenic-like behavior. The extrapyramidal motor deficits associated with the disease include stereotypic cog-wheel rigidity, balance impairment, hypokinesia, flexed posture, and shuffling gait that typically render patients immobile by their mid-teens (Hofman et al., 1999).

Imaging studies in JNCL patients have shown dysfunction in the striatum as measured by a reduction in dopamine transporter (DAT) levels and [^{18}F] fluorodopa uptake, an analog of dopamine (Ruottinen et al., 1997; Aberg et al., 2000). Once released into the synaptic cleft, dopamine activates either the D1 or D2 class of receptors. PET studies of JNCL patients showed a reduction in the striatal D1, but not D2 receptors (Rinne et al., 2002). In this study, we have investigated these

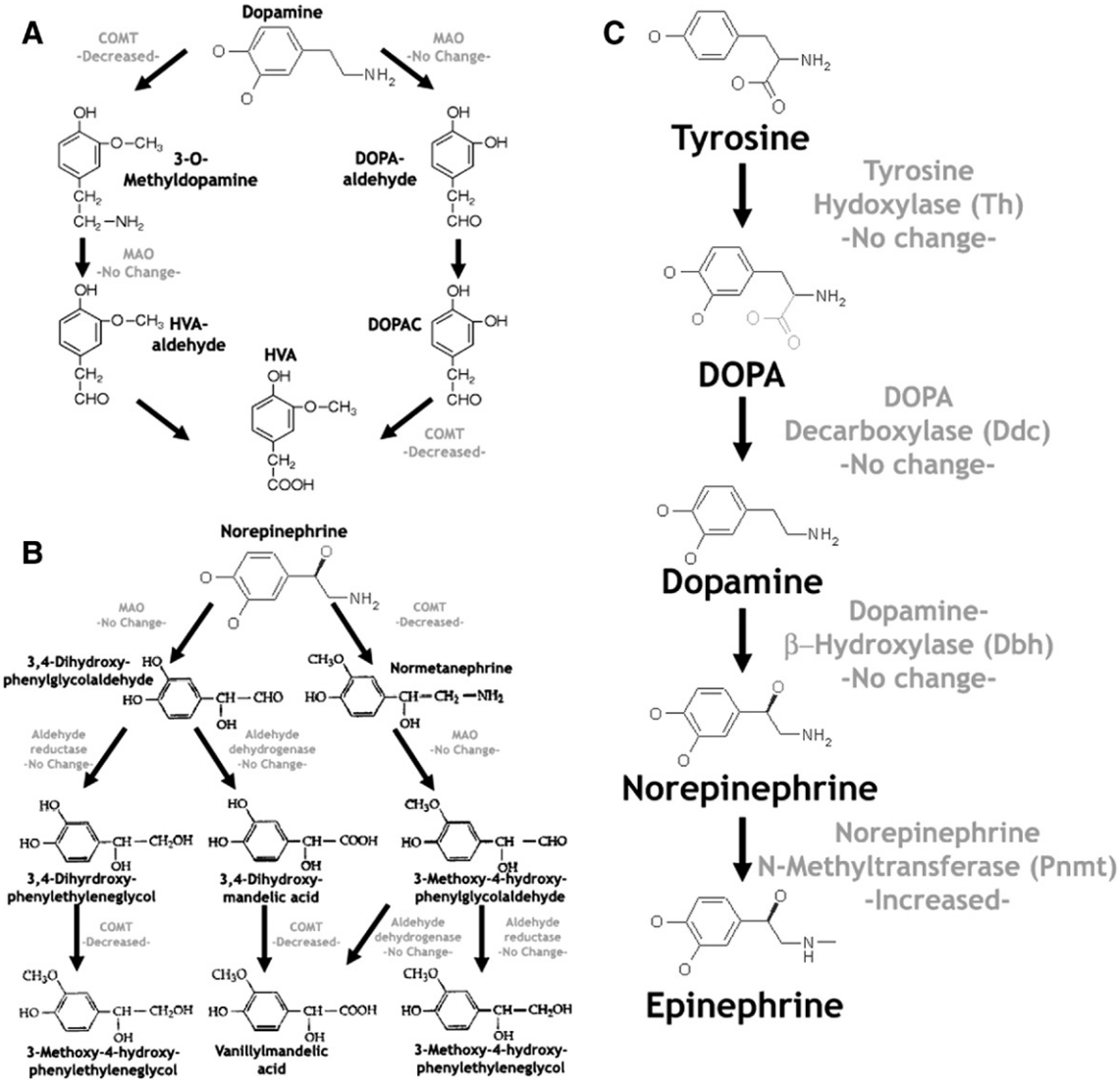

Fig. 1 – Deficits genes involved in catecholamine metabolism is restricted to a decreased in COMT in the *Cln3*$^{-/-}$ mice. Evaluation of several published microarray data sets performed on the *Cln3*$^{-/-}$ mice showed a selective down regulation in the expression of *Comt* (3.56 fold decrease, 10-week whole brain microarray) with a sparing of all other enzymes involved in catecholamine catabolism (Dopamine, A and Norepinephrine, B) (Brooks et al., 2003; Elshatory et al., 2003). Synthesis of catecholamine is achieved through conversion of tyrosine to DOPA, followed by the subsequent selective conversion to dopamine, norepinephrine, and epinephrine. Of the enzymes involved in the production of catecholamines, specifically tyrosine hydroxylase, DOPA decarboxylase, dopamine β-hydroxylase, and norephinephrine *N*-methyltransferase (*Pnmt*) none were altered in the *Cln3*$^{-/-}$ mice aside from a slight, yet significant, decrease in the level of *Pnmt*, suggesting disruption in the enzyme involved in conversion of norepinephrine to epinephrine [less than 1.5 fold change ($p \leq 0.05$, Student's *t*-test), 10-week whole brain microarray; Brooks et al., 2003] (C).