



## Mini Review

# Spinal muscular atrophy counteracted by Agrin biological NT-1654

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## Abstract

Spinal muscular atrophy (SMA) is a genetic and gravely disease, portrayed by motor neuron (MN) death, thereby leading to progressive and accelerating muscle fragility, respiratory collapse, and, in the most severe cases, it even pave the way to death. At the neuromuscular junction (NMJ), abnormally have been reported in SMA, including neurofilament (NF) aggregation at presynaptic terminals, immature and smaller endplates, lowered transmitter release, and, eventually, muscle denervation. In this review the role of Agrin in SMA is studied. This review highlights the antagonizing role of Agrin in SMA.

## Introduction

The SMA mice is treated with therapeutic Agrin biological NT-1654, from birth onwards. [1]. After the Mice were analyzed for behavior, muscle and NMJ histology, and survival there seems to a lot of improvement. Recoveries include the prevention in the size decreasing of muscle fibers, reducing of NF accumulation and the betterment in the motor behavior. Overall the infusion of Agrin reinstate the crosstalk between muscle and MNs, loitering muscular atrophy, fixing motor performance and lengthening survival.

The fatal disease Spinal muscular atrophy (SMA), caused by mutations in the telomeric gene “survival motor neuron 1” (SMN1), that consequently cannot encode SMN protein. A possible explanation for such early abnormalities was impairment of neurotrypsin/Agrin system. [2]. Among the two almost identical SMN (survival motor neuron) genes that are present on chromosome 5q13. SMA1 is only affected while SMN2 gene is not affected by the disease [3]. On the basis of age of onset and disease severity, SMA can be classified into four main clinical types (I-IV from severe to mild) [4].

## Role of Agrin

The constitution of NMJ is physiologically boosted by the neurotrypsin/Agrin system. Agrin, plays a synaptic coordinator role by easing interpolation of a nerve terminal, clustering of AChRs and maturation of NMJs [5]. This review showcases the task of Agrin in restricting muscular atrophy in SMA by the stabilization of NMJs and thus delaying disease progression, muscle atrophy and also motor impairment.

## Discussion

### Pathogenesis of SMA

SMA is a dangerous disorder due to deletion or mutation of the telomeric SMN1

gene. According to the severity of the malady. It is represented by MN degeneration resulting in the affected patient's muscular atrophy, paralysis and lessened lifespan, [3]. The SMN complex, is built of the SMN protein and 7 additional proteins (Gemin2-8), which plays a pivotal role in the assembly and biogenesis of snRNPs, and in pre-mRNA splicing. SMN is reported to have a task in the transport of axonal mRNAs in MNs, [6,7]. Besides all these, SMN is involved in the stabilization and maturation of the NMJ [8].

The transmission between the motor nerve terminal and skeletal muscle fibers takes place through NMJ as they are the particularized synapses in the peripheral nervous system (PNS). In SMA patients there is alterations in the molecular mechanisms at the NMJ. One of the earliest defects of SMA is found distal to the  $\alpha$ -MNs, at the endplate level. Studies suggest that in SMA failure of synapse maturation lead to their loss, muscular denervation and, finally, symptom onset Goulet et al. [9].

In SMA at the NMJ there is neuropathological alterations such as reduced synaptic vesicle density, altered transmission, NF accumulation, defects in synapse maintenance, immature and denervated endplates [10]. In SMA, the synaptic pathology at the NMJ is evident and appears at early symptomatic stage. The insufficiency of SMN protein deteriorate the post-natal development of NMJs.

### Therapeutic potential of Agrin biological NT-1654

The treatment with NT-1654 (Agrin) induced positive and assured effects on NMJ morphology, stimulating their maturation. In Addition to that, the accumulation of NF, a typical SMA hallmark, was meaningfully reduced after treatment. All these aspects makes it crystal clear that Agrin can contribute to reduce the impaired synaptic functions related to the SMA [11]. Due to the better innervation. And improved NMJ functionality/maturation, higher trophism of the muscles is discovered. The fiber composition is also restored by the treatment [11].

The improvements were even perceived even seen at the behavioral patterns like what happened at histological level. Weighty improvements were seen in the righting reflex, the tail suspension test and, to a small extent, the hind limb suspension test, indicating its positive effect on weakness and fatigue. Even the life span is increased in SMA patients after Agrin infusion. In short Agrin aids to delay the SMA progression, and therefore it can be identified as an effective compound (NT-1654) that could be potentially tested in human trials. As NT-1654 does not induce immune response, nor anti-Agrin antibody production it can be considered safe [12]. Agrin represent a good strategy to prevent muscle atrophy and decelerating the pathological cascade affecting MNs and NMJs in this way allowing a more extended therapeutic window. The administration of NT-1654 to SMA can compensate for the reduction of Agrin. In combination with anti-apoptosis treatment, provided boon in the disease progression in congenital muscular dystrophy, stimulating stabilization of muscle fibers, muscle growth/strength and regeneration [12].

### Concluding remarks on NT-1654 mechanism of action

In SMA, SMN deficiency is the most profound defects of the neuromuscular junctions (NMJs). Agrin being an important target of the SMN protein and that extenuating NMJ defects may be one strategy in handling human spinal muscular atrophy. In a nutshell Agrin represents a good therapeutic candidate for SMA. It can tackle Agrin deficiency and SMN-induced defects. The Agrin biological NT-1654 is a emerging promising therapy aimed at increasing SMN gene expression.

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