Amyotrophic Lateral Sclerosis (ALS) or Motor Neurone Disease: Suggested drug designs and methods to deliver Neurotrophic factors to their target sites.
Mr Casey Ray McMahon © 29th June, 2007.

Abstract: In this paper, I attempt to combine previous research data in order to design a new mechanism by which neurotrophic factors may be delivered to their target sites. Although this idea is only theoretical, it provides a novel mechanism for future drug designs involving neurotrophic factors. In this paper, I use motorneurone disease as an example, and present a theoretical drug design for this disease.

Theory: Research presented by Corcoran et al (2002) and Corcoran and Maden (1999) suggest that a defect in the retinoic acid pathway induces motorneurone disease. From this data, as well as data presented by D. Wion et al (1987) the following pathway for vitamin A, or retinoic acids, presented below in figure 1 can be derived:

![Figure 1: The retinoic acid pathway, as derived from Corcoran et al (2002), Corcoran and Maden (1999) and Wion et al (1987).](image)

Corcoran et al (2002) generated retinoid-deficient adult rats by removing retinoids from their diet. Their work showed that in the absence of retinoids, motorneurons underwent neurodegeneration, and they noticed an increase in astrocytosis as well as an accumulation of neurofilaments-pathology associated with motorneurone disease. Corcoran et al (2002) also showed that Retinaldehyde dehydrogenase enzyme 2 (Raldh-2) was not downregulated in the retinoid deficient rats or in the controls, but that this
enzyme is downregulated in human motorneurone diseased motorneurones, which would also lead to the loss of retinoic acid production (see figure 1 above).

Two families of nuclear receptors mediate the cellular affects of retinoic acids through binding with them (Karen Niederreither (1997)). These two families are RAR (α, β and γ isoforms) and RXR (α, β and γ isoforms) (Karen Niederreither (1997)). Acting as ligand-inducing transcription factors, these nuclear receptors regulate the expression of various genes. (Karen Niederreither (1997)). Hence, retinoic acids are required for proper transcription of DNA, and are essential for healthy motor neurons. From figure 1 above, Retinoic acids (all-trans-retinoic acid in particular) induce the transcription of Nerve growth factor (NGF) which can activate Raldh-2 transcription. The fact that in motorneurone diseased motorneurones, the Raldh-2 enzyme is downregulated, neurotrophins or promotors of Raldh-2 transcription would be desirable to effectively treat motorneurone disease.

One of the most significant findings in relation to motor neurone disease has been that a gene encoding the enzyme Copper/Zinc superoxide dismutase (SOD\textsubscript{1}), which is found on chromosome 21, has mutations present in 20% of familial cases of motorneurone disease, and these mutations are present in 2% of all cases of motor neurone disease. (Daniel R. Rosen et al (1993)). This enzyme catalyses the conversion of intracellular superoxide radicals, which are produced during normal cellular metabolism, to hydrogen peroxide. Other free radical scavenging enzymes then eliminate this hydrogen peroxide. Compared with other cells in the nervous system, motor neurones have a high expression of Cu/Zn superoxide dismutase, in axonal compartments and in the cell body. (Pamela J Shaw (1999)).

Yoo et al (1999) provided evidence of the involvement of the retinoid signaling pathway in regards to the expression of the SOD\textsubscript{1} gene. The SOD\textsubscript{1} promotor was shown to have a binding site for the orphan receptor peroxisome proliferator-activated receptor (PPAR), and retinoic acid, and 9-cis-Retinoic acid induced binding of PPAR to the SOD\textsubscript{1} promotor.

In regards to nerve regeneration and methods of treatment for nerve related diseases such as motor neurone disease, neurotrophins have been considered as ideal, but unfortunately the major problem with their use is that we as scientists currently don’t have methods to effectively deliver neurotrophins to the desired site of injury (Corcoran and Maden (1999)). Here, I present a method that may be used to deliver neurotrophins, as well as other drugs to neurons, including motor neurons, so that diseases like motor neurone disease may be treated.

The mechanism I propose is as follows: Neurotrophin tagging. Basically, we tag the drug of interest with a tag to trick the body into thinking that the neurotrophin is another compound, which will cause the body to deliver the neurotrophin to neurons. A sugar tag would be ideal, and I will explain why using a sugar tag will see the effective delivery of neurotrophins to neurons, hence treat if not cure diseases such as motor neurone disease. This sugar tag may also be applied to all-trans-retinoic acid and 9-cis-retinoic acid, so that these compounds may be delivered to motor neurones.

Neurones depend on sugar as their energy source- and the brain (which is composed of neurons) only stores very low levels of sugar in the form of glycogen (Brown A.M.
More importantly, glucose uptake is increased in motor neurons during times of motor neuron regeneration (Singer, P.A, and Mehler S (1983)). Singer, P.A, and Mehler S (1983) found that fasting created a deficit of glucose in rats, which resulted in an increased uptake of glucose, but rats whose nervous system was undergoing regeneration had a much higher demand for glucose, as their hypoglossal nuclei were taking up sugar. Since neurons, especially neurons undergoing regeneration (as in motor neurone disease) have such a demand for sugar, we can exploit this demand as a means to deliver drugs to damaged nerve sites- or sites in the nervous system undergoing repair. This can be achieved by attaching a sugar group, such as glucose, to the drug or substrate of interest, and since neurons metabolise sugar, they should have no problem cleaving off the sugar or glucose group from the drug of interest, which will occur once the drug has been taken up by neurons. An example of a tagged molecule is presented below.

![Figure 2: The Sugar tag neurotrophic delivery mechanism. In this Instance, I have used All-trans retinoic acid as an example, although it would be desirable to sugar tag other neurotrophic agents as well, or agents desired to be delivered to damaged neurons. It would also be desirable to sugar tag NGF (Nerve growth factor) as well as 9-cis retinoic acid to treat motor neurone disease. The structure of All-trans retinoic acid was taken from DBGET: integrated database retrieval system, Genomenet: entry number: C00777 C15493. Notice in figure 2, I attached the glucose molecule at the head of the All-trans retinoic acid molecule. This was done in order to maintain the overall linearity of the molecule, although it may be more desirable to bind the glucose in another conformation. The most effective sugar tagging confirmations will only be discovered via clinical trials or lab experimentation. Once the desired molecule is sugar tagged, so that it will be delivered to the damaged motor neurone or neurone site, it can be taken orally, although the best results may be obtained through injection.](image-url)
As previously mentioned, Neurones depend on sugar as their energy source- and the brain (which is composed of neurons) only stores very low levels of sugar in the form of glycogen (Brown A.M. (2004)). More importantly, glucose uptake is increased in motor neurons during times of motor neuron regeneration (Singer, P.A, and Mehler S (1983)). From this information, Sugar tagged molecules that we want to deliver to damaged neurons or damaged motor neurones should be taken orally or preferably injected upon waking in the morning. This is because since neurons depend upon glucose rather than glycogen for energy, neurones will consume the majority of the glucose in their vicinity during sleep creating a glucose deficit, and thus upon waking, neurones will exhibit an increased uptake of glucose, and from Singer, P.A, and Mehler S (1983), damaged neurones, or motor neurones undergoing regeneration or repair will exhibit a greater uptake of this glucose. No foods or liquids, other than water, are to be consumed for one hour after taking the sugar tagged neurotrophic factors or molecules upon waking up first thing in the morning from sleep. This is to ensure that no other glucose sources are present, so that the body will deliver the sugar tagged neurotrophic factors to neurones, rather than glucose from foods. Physical activity is not encouraged during this hour, as we want the majority of the sugar tagged neurotrophins or molecules to be delivered to neurones, not muscles. This is to ensure that the muscles don’t take up the glucose tagged neurotrophins instead of neurones. After one hour has elapsed, the patient may have breakfast as normal, and physical activity is permitted after breakfast, as the glucose stores from the breakfast meal can be used as energy for muscles.

In order to insure the effectiveness of this therapy, glucose transporters and molecules involved in glucose metabolism should also be taken in combination with the sugar tagged neurotrophic factors or molecules.

The sugar tagging neurotrophic mechanism presented in this paper is one example of a possible delivery mechanism of neurotrophic factors to their target sites. Other molecules with motor neurone specificity may also be used in place of the sugar tag. Molecular tagging may prove to be a mechanism that shall treat if not cure diseases such as motor neurone disease as well as other nerve or neurone related diseases.

References:


