4-Aminopyridine as a "Cure" for Spinal Cord Injury

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"Learning to live with paralysis is a tremendous adjustment, but now there is every reason to believe it'll be a temporary one. Human trials for effective therapies are already in the planning stages or actually underway."

- Christopher Reeve

Chronic spinal cord injury is perhaps one of the most frightening consequences of physical trauma. Damaging one's spinal cord generally produces a significant decrease in neurological function below the area of damage or paralysis, preventing the individual from functioning independently. The extent of disability varies from not being able to move one's legs (paraplegia) to the inability of controlling one's limbs, with respiration often incapacitated (as in the case of actor Christopher Reeve – complete quadriplegia). There is currently no approved therapy that can improve neurological function for individuals with chronic spinal cord injuries. As a result, most afflicted individuals are destined to remain disabled for the remainder of their lives.

A new drug called Fampridrine, currently in its final stages of trials, can potentially alter this bleak outlook. Fampridine allows for very exciting possibilities. During its clinical assessment, many patients with spinal cord damage regained sensation, and in some cases even function, to limbs and areas of the body that were believed to be desensitized. This undoubtedly renews hope for those who have sustained chronic spinal cord injuries that have resulted in the loss of neurological function.

Fampridine (4-aminopyridine or 4-AP) is a potassium channel-blocking agent that is responsible for eliciting conduction along fibres that have been demyelinated due to a spinal cord injury (Hayes et al., 1993). Patients afflicted with such injuries retain some axons. These surviving axons are often damaged and lose part of their myelin sheath. Myelin is an insulating structure that aids in the conduction of electrical impulses along the axon. When the myelin portion of an axon is damaged, or when demyelination occurs, a large proportion of potassium channels are exposed and the associated potassium ions leak out, causing the affected axon to "short circuit" ("The mechanism", 2003). Although demyelinated axons are physically living, they are unable to transmit sensory or motor impulses from the brain to their ultimate destinations, and hence, the affected individual basically loses the sensation and movement of the particular area ("Research", 2003).

Fampridine effectively counteracts the effects of demyelination caused by spinal cord injuries (Hayes, 2002). Essentially, it restores the ability of damaged nerves to conduct electrical impulses by blocking the exposed potassium channels in the demyelinated axons, thus restoring the normal flow of potassium ions (Potter et al., 1998) (Fig. 1). This blocking ability renders the cell more excitable, and therefore amplifies the impulse signal so that it can travel along the nerve past the demyelinated area (Hansebout et al., 1993). Currently, Fampridine is given in the form of Fampridine-SR, where a sustained release (SR) mechanism allows the gradual release of 4-AP and maintains a consistent level in the blood. This ensures that the drug's effect is not an ephemeral, and that the patient will benefit for a longer period of time ("Research", 2003).

What is wonderful about 4-AP is that it is not simply a theoretical solution like many trial medications – it really does work. When speaking with Dr. Hansebout, Professor Emeritus of McMaster Health Sciences, who was one of the first people to actually participate in the drug administration in spinal cord injury patients, the response was clear – Fampridine was helping. Dr. Hansebout noted that "patients who could not move their legs at all noticed that, after receiving the drug, they could move them up and down quite substantially, relatively speaking". He went on to add that patients with moderate (incomplete) injuries had some enhancement of "sexual function, better bladder and bowel control, improved circulation [they could breathe far better], and experienced a reduction in pain and spastic movement." Dr. Hansebout also remarked on 4-AP's interesting history. Fampridine was apparently discovered in "eastern Europe, as many farmers in the area used it as bird repellant in the 1970's." After ingesting the chemical, Dr. Hansebout said "birds received an unpleasant shock to their nervous system, and never returned to the area again. Over the next decade, scientists studied the drug and eventually came to the conclusion that it is a voltage enhancer, and began conducting experiments with mice. Subsequently, its role as a conduction augmenter was hypothesized to alleviate the pain from conditions that reduce the transmission of electrical impulses. However, the scientists involved were not doctors and therefore

not allowed to test on humans. Physicians were required to perform clinical trials, thus commenced my own involvement."

During the first human trials, an immediate-release type of the drug was administered to patients. Due to the limited trial period, only a few patients exhibited noticeable improvement in neurologic function (Hayes, 2002). In addition, the impact of Fampridine being delivered in a single, often highly concentrated dose, resulted in negative side effects such as nausea, depression, irritability and diarrhea (Hansebout et al., 1993). Once the sustained-release form (Fampridine-SR) was developed and administered to patients, it appeared that the majority of individuals suffering from moderate forms of chronic spinal cord injury enjoyed improved neurologic function below the area of injury, an effect that would never have been obtained otherwise (Hansebout et al., 1993). To date, trials have yet to give rise to noticeable improvement in neurologic function in patients suffering from severe chronic spinal cord injuries and complete paraplegia and quadriplegia (Hayes, 1993). However, Fampridine is continuously being researched, and similar cases, as well long-term usage, is also being investigated ("Research", 2003).

Fampridine is also being studied for its potential in treating people with multiple sclerosis. Thus far, the results have been incredible. In 1997, a double-blind, cross-over trial of the drug in MS patients saw that 90% of those given the drug benefited noticeably compared to those who received the placebo (Schwid et al., 1997).

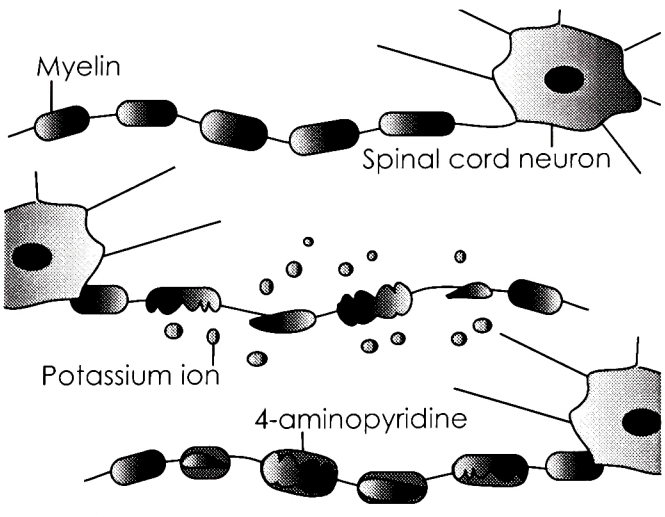

Figure 1

In many spinal cord injuries myelin surrounding nerve cells are damaged. This causes potassium ions to leak out, preventing the neuron from transmitting signals. The drug 4-aminopyridine blocks the pores in the damaged myelin, thus allowing transmission when the cell becomes excited.

Motor function was substantially enhanced and MS symptoms were significantly diminished. Another similar study conducted in England in 2000 suggested that 4-AP also improved mechanisms like potentiation of synaptic transmission, and increased skeletal muscle twitch tension, effects that do not even involve the target demyelinated axons (Smith et al., 2000). Such findings could conceivably lead to the use of Fampridine to treat other neurological disorders (Smith et al., 2000).

The effectiveness of 4-Aminopyridine in treating patients suffering from chronic spinal cord injuries and other neurological disorders is to date unparalleled. Once it is made available to the public, its application will become an important element in the concert of treatment methods used for spinal cord injury patients. These methods include spinal cord cell grafting, a technique that aids the regeneration of motor and sensory neurons, and implantation of AIT-082, a synthetic purine used to supplement adenosine and guanosine purine loss due to spinal cord injury. Adenosine and guanosine signal nerve cells to protect themselves from further damage, and also act as chemical messengers to signal cells like astrocytes and glia to release trophic factors ("The role of purines", 2003).

Fampridine is a truly amazing drug, and those suffering from spinal cord injury, multiple sclerosis and other neurological disorders are extremely fortunate to be on the brink of gaining access to this effective treatment. As yet, Fampridine is not a comprehensive cure because it will not allow a paraplegic individual to walk again; however, it is certainly a step in the right direction. McMaster is quite fortunate in that much of the corroborative evidence obtained and groundbreaking research involved with this revolutionary treatment took place within its hospitals. As well, there are many organizations and institutions like the Canadian and American Spinal Research Organization and the Christopher Reeve Paralysis Foundation that are actively involved in ensuring that Fampridine is made available to those who need it. Granted, much research is still underway, but at least for now, there is hope for those who suffer from conditions and disorders that inhibit neurological function. M