Neuropathy

Excerpt from www.canadianneuropathyassociation.org:

Neuropathy – what Is It?

Neuropathy is the disease of the nervous system. Neuropathy is a disturbance in the function of a nerve or particular group of nerves. The three major forms of nerve damage are: ***peripheral neuropathy***, ***mononeuropathy***, and ***autonomic neuropathy***. The most common form is peripheral neuropathy, which mainly affects the feet and legs. Any one of these may cause ***Neuropathic Pain***. Neuropathy can lead to disability, amputation, decreased ambulation as well as foot and leg ulceration because of loss or damage to nerves which feel sensation in the lower limbs. Another reason for the disability is due to the changes that can occur in the biomechanics of feet and legs, leading to an increased risk of ulcers.

Peripheral Neuropathy

The term peripheral neuropathy describes a problem with the functioning of the nerves outside of the spinal cord. The symptoms of a neuropathy may include numbness, weakness, burning pain (especially at night), and loss of reflexes. The pain may be severe and disabling. There are many possible causes of peripheral neuropathy. Some of the most common causes include repetitive activities such as typing or working on an assembly line. In this case, the neuropathy may be isolated to the upper extremities, such as with carpal tunnel syndrome. Pressure on a nerve can cause a peripheral neuropathy. For example, pressure on a nerve that comes out from the groin to the skin in front of the upper thigh can cause burning and tingling in this location. This particular problem is called meralgia paresthetica and can be caused by wearing a tight belt or other restrictive clothing. Additionally, it can result from being overweight or pregnant. Many illnesses can result in peripheral neuropathy. Some examples include diabetes, syphilis, AIDS, and kidney failure. Other causes include nutritional deficiencies, such as B-12 and folate deficiency, medications and chemical exposures. Medications known to cause peripheral neuropathy, include several AIDS drugs (DDC and DDI),

antibiotics (metronidazole, an antibiotic used for Crohn's disease, isoniazid used for TB), gold compounds (used for rheumatoid arthritis), some chemotherapy drugs (such as vincristine and others) and many others. Chemicals known to cause peripheral neuropathy include alcohol, lead, arsenic, mercury and organophosphate pesticides. Some peripheral neuropathies are associated with diseases which are inherited (hereditary). Others are related to infectious processes (such as Guillian-Barre syndrome).

Mononeuropathy

Mononeuropathy is damage to a single peripheral nerve. Physical injury is the most common cause of a mononeuropathy. Often, the injury is caused by prolonged pressure on a nerve that runs close to the surface of the body near a bony prominence, such as a nerve in an elbow, a shoulder, a wrist, or a knee. Pressure on a nerve during a long, sound sleep (especially in alcoholics) may be prolonged enough to cause damage. Pressure may result from a misfitting cast, improper use of crutches, or staying in a cramped position for a long time, such as when gardening or when playing cards with the elbows resting on a table. Damage due to pressure may also occur in people who are under anesthesia for surgery, in those who are bedridden (particularly older people), and in those who are paralyzed. Less commonly, strenuous activities, accidents, prolonged exposure to cold or heat, or radiation therapy for cancer may also damage a nerve. Repeated injuries, such as those due to tight gripping of small tools or to excessive vibration from an air hammer, can also damage nerves. Infections, such as leprosy and Lyme disease, may destroy a nerve, causing mononeuropathy. Cancer may cause mononeuropathy by directly invading a nerve. Some toxic substances and some drugs can cause mononeuropathy. Certain peripheral nerves are more vulnerable to injury. Examples are the median nerve in the wrist, resulting in carpal tunnel syndrome, the ulnar nerve in the elbow, the radial nerve in the upper arm, and the peroneal nerve near the knee. When the Foot's Asleep A sleeping foot can be considered a temporary neuropathy. The foot falls asleep when the nerve supplying it is compressed. Compression interferes with the blood supply to the nerve, making the nerve give off abnormal signals (a pins-and-needles sensation), called a paresthesia. Moving around relieves the compression and restores the blood supply. As a result, nerve function resumes, and the pins-and-needles sensation stops.

Autonomic Neuropathy

Autonomic neuropathy is a group of symptoms caused by damage to nerves that regulate blood pressure, heart rate, bowel and bladder emptying, digestion, and other body functions. Autonomic neuropathy is a form of peripheral neuropathy. Autonomic neuropathy is a group of symptoms, not a specific disease. There are many causes. Autonomic neuropathy involves damage to the nerves that run through a part of the peripheral nervous system. The peripheral nervous system includes the nerves used for communication to and from the brain and spinal cord (central nervous system) and all other parts of the body, including the internal organs, muscles, skin, and blood vessels. Damage to the autonomic nerves causes abnormal or decreased function of the areas connected to the problem nerve. For example, damage to the nerves of the gastrointestinal tract makes it harder to move food during digestion (decreased gastric motility). Damage to the nerves supplying blood vessels causes problems with blood pressure and body temperature.

Autonomic neuropathy is associated with the following:

Alcoholic neuropathy * Diabetic neuropathy * Parkinson's disease * Disorders involving sclerosis of tissues * Surgery or injury involving the nerves * Use of anticholinergic medications * Symptoms Swollen abdomen * Heat intolerance, induced by exercise * Nausea after eating * Vomiting of undigested food * Early satiety (feeling full after only a few bites) * Unintentional weight loss of more than 5% of body weight * Male impotence * Diarrhea * Constipation * Dizziness that occurs when standing up * Blood pressure changes with position * Urinary incontinence (overflow incontinence) * Difficulty beginning to urinate * Feeling of incomplete bladder emptying * Fainting* Abnormal sweating

Non-psychoactive CB_2 cannabinoid agonists stimulate neural progenitor proliferation

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Abstract

Cannabinoids, the active components of marijuana and their endogenous counterparts, act on the brain and many other organs through the widely expressed CB_1 cannabinoid receptor. In contrast, the CB_2 cannabinoid receptor is abundant in the immune system and shows a restricted expression pattern in brain cells. CB_2-selective agonists are, therefore, very attractive therapeutic agents as they do not cause CB_1-mediated psychoactive effects. CB_2 receptor expression in brain has been partially examined in differentiated cells, while its presence and function in neural progenitor cells remain unknown. Here we show that the CB_2 receptor is expressed, both in vitro and in vivo, in neural progenitors from late embryonic stages to adult brain. Selective pharmacological activation of the CB_2 receptor in vitro promotes neural progenitor cell proliferation and neurosphere generation, an action that is impaired in CB_2-deficient cells. Accordingly, in vivo experiments evidence that hippocampal progenitor proliferation is increased by administration of the CB_2-selective agonist HU-308. Moreover, impaired progenitor proliferation was observed in CB_2-deficient mice both in normal conditions and on kainate-induced excitotoxicity. These findings provide a novel physiological role for the CB_2 cannabinoid receptor and open a novel therapeutic avenue for manipulating neural progenitor cell fate.—Palazuelos, J., Aguado, T., Egia, A., Mechoulam, R., Guzmán, M., Galve-Roperh, I. Non-psychoactive CB_2 cannabinoid agonists stimulate neural progenitor proliferation.

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Prevention of Paclitaxel-Induced Neuropathy Through Activation of the Central Cannabinoid Type 2 Receptor System

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Abstract

BACKGROUND: Peripheral neuropathy is a major dose-limiting toxicity of chemotherapy, especially after multiple courses of paclitaxel. The development of paclitaxel-induced neuropathy is associated with the activation of microglia followed by the activation and proliferation of astrocytes, and the expression and release of proinflammatory cytokines in the spinal dorsal horn. Cannabinoid type 2 (CB_2) receptors are expressed in the microglia in neurodegenerative disease models.

METHODS: To explore the potential of CB_2 agonists for preventing paclitaxel-induced neuropathy, we designed and synthesized a novel CB_2-selective agonist, namely, MDA7. The effect of MDA7 in preventing paclitaxel-induced allodynia was assessed in rats and in $CB_2^{+/+}$ and $CB_2^{-/-}$ mice. We hypothesized that the CB_2 receptor functions in a negative-feedback loop and that early MDA7 administration can blunt the neuroinflammatory response to paclitaxel and prevent mechanical allodynia through interference with specific signaling pathways.

RESULTS: We found that MDA7 prevents paclitaxel-induced mechanical allodynia in rats and mice in a dose- and time-

dependent manner without compromising paclitaxel's antineoplastic effect. MDA7's neuroprotective effect was absent in $CB_{2}^{-/-}$ mice and was blocked by CB_2 antagonists, suggesting that MDA7's action directly involves CB_2 receptor activation. MDA7 treatment was found to interfere with early events in the paclitaxel-induced neuroinflammatory response as evidenced by relatively reduced toll-like receptor and CB_2 expression in the lumbar spinal cord, reduced levels of extracellular signal-regulated kinase 1/2 activity, reduced numbers of activated microglia and astrocytes, and reduced secretion of proinflammatory mediators in vivo and in in vitro models.

CONCLUSIONS: Our findings suggest an innovative therapeutic approach to prevent chemotherapy-induced neuropathy and may permit more aggressive use of active chemotherapeutic regimens with reduced long-term sequelae.

http://www.anesthesia-analgesia.org/content/114/5/1104.abstract