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REVIEW ARTICLE

Role of protease inhibitors in the pathogenesis of alcoholic neuropathy

Papel de los inhibidores de la proteasa en la patogénesis de la neuropatía alcohólica

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ABSTRACT

Background: alcoholic neuropathy is a common complication among patients with alcohol abuse disorder. It is often asymptomatic and the frequency of occurrence varies. We propose that the deficit of protease inhibitors could be a causal factor of alcoholic neuropathy. If this is true, it would contribute to understanding of the pathophysiology, explain variability in individual response, and explain variability in individual response, and facilitate the search for prevention therapy.
Development: alcoholic neuropathy is characterized by a pattern of symmetrical polyneuropathy with great involvement of the lower extremities. The mechanisms of axonal degeneration due to alcohol consumption are still unclear. It is known that alcohol inhibits protection mechanisms of the nervous system. Here, we discuss that the deficit of protease inhibitors could be a causal factor in the pathogenesis of alcoholic neuropathy. If this is true, it would contribute to an understanding of the pathophysiology, explain variability in individual response, and facilitate the search for prevention therapy.
Conclusions: the protease inhibitors play a significant role in the origin of peripheral neuropathies. There is strong evidence to suggest that proteases and their inhibitors are related to processes that allow the development and maintenance of peripheral nerves, and alterations in their proportions favor the development of anomalies in such structures. The mechanisms through which these molecules trigger the disease are unclear in most cases. An increase in the number of investigations in this area would undoubtedly contribute to preventing and combating a disease which strikes a significant number of people.

Keywords: Alcohol; Protease inhibitors; Alcoholic Neuropathy; Alcoholic Neuropathy/Pathogenesis; Peripheral Neuropathy.

RESUMEN

Antecedentes: la neuropatía alcohólica es una complicación común entre los pacientes con trastorno por abuso de alcohol. Suele ser asintomática y su frecuencia de aparición es variable. Proponemos que el déficit de inhibidores de la proteasa podría ser un factor causal de la neuropatía alcohólica. Si esto es cierto, contribuiría a la comprensión de la fisiopatología, explicaría la variabilidad en la respuesta individual y facilitaría la búsqueda de una terapia de prevención.

Desarrollo: la neuropatía alcohólica se caracteriza por un patrón de polineuropatía simétrica con gran afectación de las extremidades inferiores. Los mecanismos de degeneración axonal debidos al consumo de alcohol aún no están claros. Se sabe que el alcohol inhibe los mecanismos de protección del sistema nervioso.
Conclusiones: los inhibidores de la proteasa juegan un papel importante en el origen de las neuropatías periféricas. Existen fuertes evidencias que sugieren que las proteasas y sus inhibidores están relacionados con los procesos que permiten el desarrollo y mantenimiento de los nervios periféricos, y las alteraciones en sus proporciones favorecen el desarrollo de anomalías en dichas estructuras. Los mecanismos por los que estas moléculas desencadenan la enfermedad no están claros en la mayoría de los casos. Un aumento de las investigaciones en este ámbito contribuiría sin duda a prevenir y combatir una enfermedad que afecta a un número importante de personas.

Palabras clave: Alcohol; Inhibidores de la Proteasa; Neuropatía Alcohólica; Neuropatía Alcohólica/Patogénesis; Neuropatía Periférica

INTRODUCTION

Substance addiction is one of the main scourges plaguing contemporary society. However, conditioned by the deterioration of social behaviors of the modern world, individuals begin drug use at increasingly younger ages.

A significant number of substances that affect the nervous system are easily obtainable despite being prohibited by law. However, there are others that are permitted from a legal point of view, even if their toxicity to human health is known. Moreover, people consume them steadily enough to ruin their health; such is the case of alcohol use disorder, defined as a chronic behavioral disorder manifested by repeated alcohol consumption that is excessive according to social and dietary norms of the community and eventually interferes with one's health or economic and social functions.[1] It has a number of implications for the individual; in addition to harming one's social image, it has direct implications on one's quality of health and, therefore, quality of life.

One of the disorders to which individuals who consume alcohol consistently over time are exposed is alcoholic neuropathy, which is characterized by peripheral nerve dysfunction caused by alcohol consumption. However, the origin of the disease is yet unclear. As with most clinical entities, it involves processes which different facets that are difficult to imagine.

Alcoholic neuropathy is a common complication among patients with alcohol use disorder. It is often asymptomatic and the frequency of occurrence varies.[2,3] It is characterized by a pattern of symmetrical polyneuropathy with great involvement of the lower extremities.[4,5] The mechanisms of axonal degeneration due to alcohol consumption are still unclear. It is known that alcohol inhibits protection mechanisms of the nervous system[6] and that alcohol can induce neuroapoptosis during the fetal stage.[7,8]

It has been shown in animal models that chronic alcohol consumption is a factor that impedes the regeneration of peripheral nerves and the increase of nerve innervations

Although it is clear that alcohol directly affects cells of the central and peripheral nervous system, some researchers argue that neuronal damage is more related to nutritional deficiency, specifically thiamine deficiency,[9] than the direct toxic effect of alcohol.

Thiamine deficiency neuropathy and alcoholic neuropathy share common clinical features, which has led to the conclusion that both neuropathies are the same entity that occurs due to thiamine deficiency.[10,11] Ultimately, the source of this vitamin deficiency would be what makes the difference.

Hypothesis: the deficit of protease inhibitors could be a causal factor of alcoholic neuropathy. If this is true, it would contribute to understanding of the pathophysiology, explain variability in individual response, and explain variability in individual response, and facilitate the search for prevention therapy.

DEVELOPMENT

Rationale for the hypothesis: firstly, it should be noted that the pathogenesis of alcoholic neuropathy is a field of research with many unknowns. Alcoholic neuropathy can occur due to the combination of the toxic effects of alcohol on the nervous system and thiamine deficiency. As mentioned previously, thiamine deficiency plays an important role in the development of alcoholic neuropathy, the effects of alcohol on the action of this vitamin in the body directly affect absorption or oxidative metabolism, which contributes to its deficiency in the case of patients with alcohol use disorder,[12,13] in addition to the tendency of patients with alcohol use disorder to prioritize alcohol over food.[14]

Thiamine deficiency damages the nervous system through various mechanisms, one of which is related to increased activity of PKR (protein kinase R), an enzyme that activates double-stranded RNA. Typically, this protein plays an important role in the elimination of viral infections; however, its participation in the induction of neuronal death has been demonstrated. Although the mechanism by which it facilitates this effect has not been clearly shown, it is known that PKR is related to the impairment of oxidative metabolism.[15,16,17]

Few reports refer to the effect of the neurotoxic mechanism on peripheral nerves; most of these mechanisms cause brain damage. It is known that in the brains of macaques during the fetal state, alcohol is capable of inducing the death of these cells.[18] It has also been reported that alcohol is able to block endocytosis in neuronal cells, which is required for cell turnover mechanisms and other important cell functions.[19,20] Undoubtedly, these mechanisms could give rise to the origin of dissimilar cellular and molecular abnormalities that affect overall cell function and produce neuropathic phenomena, as in the case of alcoholic neuropathy.

Evaluation of the hypothesis

Exogenous inhibitors

There is a substantial body of evidence relating protease inhibitor levels with the risk of deterioration of peripheral nerves. However, this link is not always manifested in the same way; some favor the development of neuropathic processes, while others impede them. Clearly, these differences may be related to the mechanisms of action of these inhibitors.

One of the side effects of the new treatment of multiple myeloma with proteasome inhibitors and protease is peripheral neuropathy;[21,22,23,24] however, it is important to note that this treatment induces apoptosis by inhibiting proteolysis via the proteasome. It also inhibits the NF-KB pathway and, consequently, the synthesis and activity of neurotrophins,[25,26,27] which have a role in the regeneration of Schwann cells and in the repair of neuronal damage.[28] The foregoing indicates that the onset of neuropathy is related to the supply of protease inhibitors as drugs.

It is important to mention the high prevalence of neuropathy in patients with HIV who are undergoing antiretroviral therapy. Regardless of their efficacy in inhibiting viral replication, these drugs have side effects such as neuropathy and metabolic disorders.[29,30,31]

Exposure to these drugs may enhance neuronal damage through loss of trophic factors derived from macrophages.[31,32,33]

Several studies show that the use of protease inhibitors have a preventive effect on the onset of the degeneration of peripheral nerves, as in the case of vildagliptin, which is an inhibitor of dipeptidyl peptidase IV and has a preventive effect in polyneuropathy in diabetic rats.[34] Another important point is the inhibitory effect of treatment of hypertension with angiotensin-converting enzyme (ACE) inhibitors on the progression of diabetic neuropathy.[35,36,37,38] An experiment conducted in rats showed that

captopril reduced the degree of deterioration of peripheral nerves subjected to vibration[39] and that ACE inhibitors have an inhibitory effect on matrix metalloproteinase (MMP).[40,41,42] However, in this case it is possible that this protective role is also related to the prevention of damage related to the velocity of blood flow which could have a negative effect on the development and maintenance of peripheral nerves.

Endogenous inhibitors

MMPs are an endopeptidase group originally described as proteases that degrade extracellular matrix proteins, but it is now known that their role is much more important and has been linked to the process of cell damage and regeneration of nervous system structures.[43] It has been found that following damage to the myelin sheath, MMP inhibition has a positive effect on Schwann cell regeneration [43,44]. For patients with systemic lupus, erythematosus has been associated with the onset of peripheral neuropathy with high serum levels of metalloproteinase.[45]

During the Cuban epidemic neuropathy, alpha1 antitrypsin deficiency was reported at the initial stage of the disease, which suggests a relationship between protease inhibitors and the pathophysiology of the disease.[46] Another point of contact linking inhibitors of endogenous protease neuropathic processes is the fact that matrix metalloproteinases can degrade alpha-1 antitrypsin, inducing supra-regulation of these proteases[47,48] which could be related to the genesis of neuropathy due to damage caused by these proteins. Furthermore, it has been reported that certain variants of the gene encoding for this inhibitor, in addition to being related to liver and lung damage, are associated with white matter abnormalities or multisystem memory disorders.[49]

Behavior of protease inhibitors in patients with alcohol use disorder

Alpha-1 antitrypsin

There are no reports that show the relationship between protease inhibitors and alcoholic neuropathy. It has only been reported that in alcoholic myopathy, levels of protein synthesis decrease and protease levels are low or unchanged.[50] However, it would be interesting to inquire as to whether alcohol has any direct effect on the mechanisms of synthesis of endogenous protease inhibitors. A study conducted in 2007 showed elevated levels of alpha-1 antitrypsin in patients with alcohol use disorder;[51] however, in this report there are no references to neuropathic processes, so it would be inappropriate to make any assumptions. It has been reported that genetic deficiency of alpha-1 antitrypsin in patients with alcohol use disorder may influence the development of cirrhosis of the liver and emphysema.[52] This could be related to high specific activity proteases, as has been reported for these diseases,[53,54] some of which could have an impact on the development of neuropathic processes through different mechanisms.

MMP inhibitors

As mentioned previously, MMP has a negative effect on the mitotic processes of Schwann cells. There is evidence to support the thesis that these enzymes are activated by mediators of the immune system such as TNF induced by infections, which can increase these enzymes and damage these (Schwann) cells, with a significant effect on the demyelination of peripheral nerves.[44,55,56,57]

High levels of TNF, which may somehow determine the onset of neurodegeneration, have been reported in patients with alcohol use disorder.[58] It has been shown that together with the increased concentration of TNF and MMPs, the expression of TLR4 increases;[59] therefore, it can be stated that TNF and MMP are involved in inducing neuroinflammation and the death of glial cells.[60]

It has also been reported that in rodent models, deficiency of this protein induces resistance to chronic alcohol consumption and prevents activation of cell death mechanisms,[60,61] indicating an important role of these molecules in alcohol-induced pathological processes.

A known MMP inhibitor is TIMP-1, which belongs to the family of multifunctional proteins that not only regulate MMP activity, but also cell growth, migration, proliferation and apoptosis in non-nervous

tissues.[62]

It would be logical to expect that in the case of alcoholic neuropathy, serum levels of this compound would be low, causing irreversible neurological damage. However, no report relating levels of this inhibitor to chronic alcohol consumption has been found. Increased levels of matrix metalloproteinases MMP-9, which have been linked to the onset of heart disease, have been seen in patients with alcohol use disorder.[63,64]

In the case of diabetic neuropathy, decreased levels of TIMP-1 been observed, which is another point indicating that protease inhibitors play an important role in the pathogenesis of neuropathy.[65] There is evidence to support the fact that in patients with alcohol use disorder, matrix metalloproteinases can induce damage to the blood brain barrier. It is assumed that this is one mechanism through which alcohol may be able to induce neurodegeneration.[66]

Calpain inhibitors

Another protease related to neurodegeneration is calpain-dependent Ca2+.[67,68] Increased activity of this enzyme is associated with apoptotic processes of different cell types, among which are nervous system cells.[69] In a specific type of neuropathy, it has been shown that pre-treatment with inhibitors of this enzyme decreases symptoms of the disease such as hyperalgesia and allodynia. It has also been observed that sciatic nerve damage is associated with activation of this enzyme,[70,71] and that the use of inhibitors of this protein corrects neurological disorders in diabetic rats.[72]

Furthermore, it was found that in animal models, using calpain inhibitors prevents the development of neuropathic processes, and in spinal cord transplantation, it has been noted that treatment with this inhibitor prevents damage post-transplant.[73,74]

In animal models, it has been shown that chronic and acute alcohol consumption increase calpain activity, which is considered to play an important role in the neurotoxicity of ethanol.[75,76]

CONCLUSIONS

Protease inhibitors play a significant role in the origin of peripheral neuropathies. There is strong evidence to suggest that proteases and their inhibitors are related to processes that allow the development and maintenance of peripheral nerves, and alterations in their proportions favor the development of anomalies in such structures. The mechanisms through which these molecules trigger the disease are unclear in most cases. The proposed mechanisms are highly divergent between different authors. In the specific case of alcoholic polyneuropathy, there is little or no information available directly linking protease inhibitors to the disease; evidently, this is a field that is virtually unexplored. An increase in the number of investigations in this area would undoubtedly contribute to preventing and combating a disease which strikes a significant number of people.

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