Chapter 5

The Role of Nucleotides in Glial Cells during Peripheral Nerve Trauma and Compressive Disorders

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Additional information is available at the end of the chapter

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Abstract

Studies have shown that the administration of drugs containing pyrimidine nucleotides, such as uridine triphosphate (UTP) and cytidine monophosphate (CMP), has been effective in pain-intensity reductions in patients with painful conditions as diabetic neuropathy, back pain, and cervical and trauma-compressive changes. The combination of pyrimidine nucleotides UTP and CMP is part of a peripheral neuro-regenerative process. Its pharmacological properties are stimulation of nerve cells proteins synthesis, nerve cell membranes synthesis, myelin sheaths synthesis, and neurite sprouting through P2Y receptors activation. Herein, chapter will be discussed the combination of UTP and CMP, and in some cases, the inclusion of cobalamin (B12 vitamin) that appears to have analgesic effects in neuropathic pain secondary to spine structural disorders assigned to a complex pharmacodynamic. The mechanisms involved can be both indirect (protein synthesis in nerve cells, myelin synthesis, synthesis of MBP, etc.) and direct (P2Y receptor stimulation).

Keywords: nerve injury, nucleotides, peripheral regeneration, purinergic receptors, Schwann cells

1. Introduction

Neuropathic pain is defined as a pain caused by primary lesion or damage to the central or peripheral nervous system and is an issue that has not been thoroughly studied or resolved. Damage may result of compression, cutting, ischemic or metabolic disorders,

cellular infiltration, or a combination of these factors [1]. About 50–90% of adults under 45 years, at some point of their lives, have a spine pain experience, especially in the lower back, being the main cause of disability [2]. Studies have shown that the administration of drugs containing pyrimidine nucleotides, such as uridine triphosphate (UTP) (**Figure 1A**) and cytidine monophosphate (CMP) (**Figure 1B**), has been effective reductions in pain intensity that have been reported in patients with painful conditions such as diabetic neuropathy, back pain, cervical pain, and trauma-compressive disorders [3–6]. The pyrimidine nucleotides UTP and CMP are part of a peripheral neuro-regenerative combination. Its pharmacological properties are stimulation of nerve cell synthesis of proteins, synthesis of nerve cell membranes, synthesis of myelin sheaths, and neurite sprouting through P2Y receptors stimulation [7]. Regarding analgesic capacity itself, pharmacological properties of two pyrimidinic nucleotides were experimentally demonstrated by Okada et al. (2010), which concluded that the activation of UTP-sensitive P2Y2 and/or P2Y4 receptors produces inhibitory effects on spinal pain transmission [8].

To better understand the role of nucleotides on peripheral nervous disorders, first, we need to get a brief review on peripheral nervous morphology as well as have the regeneration steps highlighted. The aim of this chapter is to clarify all steps and functions of those components in regeneration, focused on the relationship among nucleotides and glial cells.

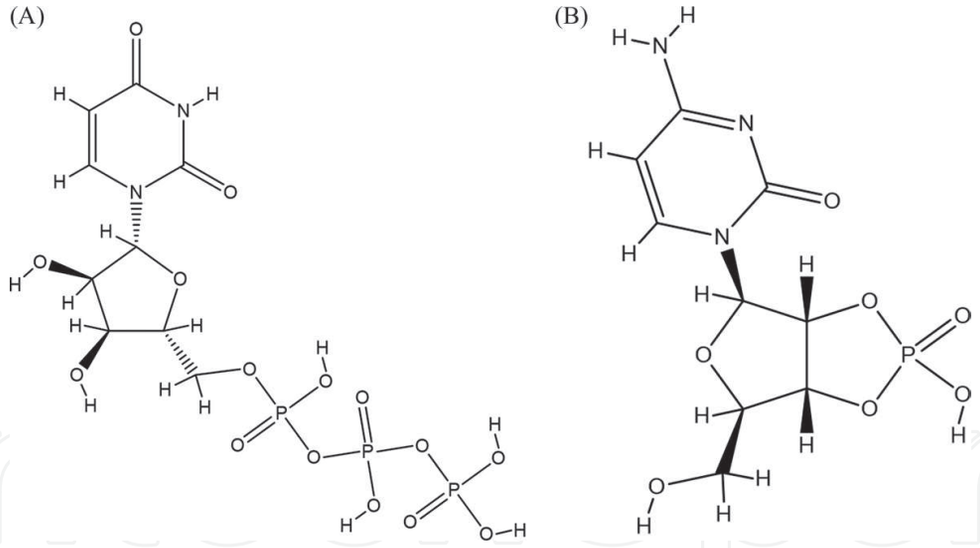

Figure 1. A—molecular structure of uridine triphosphate; **B**—molecular structure of cytidine monophosphate (CMP).

2. Peripheral nervous system

The peripheral nervous system (PNS) consists of (1) peripheral nerves, composed of the set of nerve fibers joined by connective tissue and (2) their motor and sensorial endings. In addition, nerves can be divided as their innervation—cranial or spinal—and as the types of fibers that compose them—sensorial, motor, or mixed [9].

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The nervous tissue mainly consists of neurons and neuroglia, which helps in neuronal or defense activity, aiding in the support and protection of neurons. Each neuron has a cell body (soma) from which the axon radiates the nerve impulses to its synaptic terminal, and the dendrites, which receive and transmit synaptic information in the body of nerve cells [10]. In addition, some axons are surrounded by a myelin sheath, which in the central nervous system (CNS), is produced by oligodendrocytes and, in the PNS, by Schwann cells (SCs) [11]. In this way, the fibers are capable of conducting the electrical impulse, being called afferents when conducting to the CNS, or efferent when conduction starts from the CNS to the target organs [10].

3. Myelination

The myelinated fibers of the PNS are composed of a single axon, which is individually wrapped by a single SC [11, 12]. The membrane of SC surrounds the fiber to form a multilaminated myelin sheath [9] (**Figure 2**), isolating the axon and helping in the saltatory conduction of electrical signals [11].

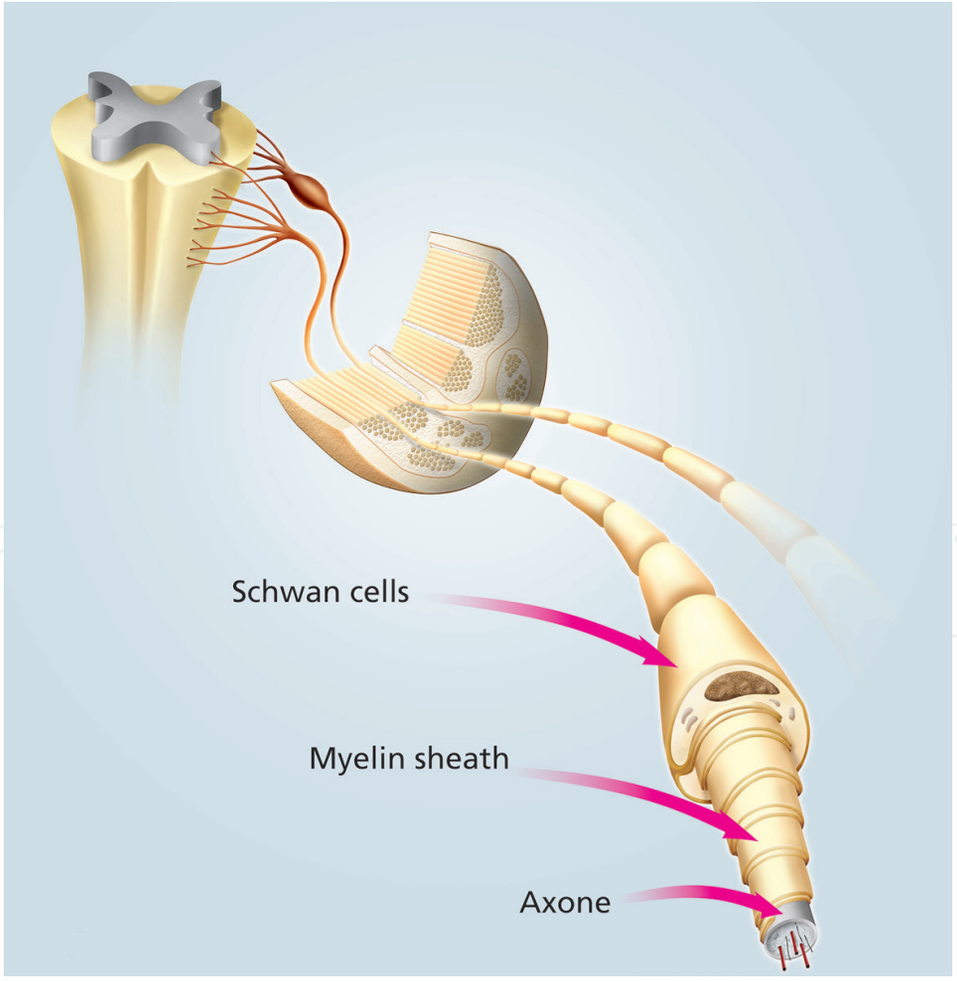

Figure 2. Diagram representing the origin of the neuroglial structural components.

Throughout the maturation process, all immature SCs have the same potential for development. When they are associated with axons of greater caliber (above 1 μm), they become myelinating SCs, and if they are associated with axons of small diameter, they become mature nonmyelinating SCs [13]. In this process, there is a fundamental participation of neurotrophin (NT), as nerve growth factor (NGF), which serves as a signaling for tyrosine kinase family receptors (TrkA) on axon, promoting an axonal diameter growth. Thus, NGF indirectly participates in myelinization of the axon. Besides that, it was observed that, during myelination, some cell adhesion molecules are downregulated, such as L1 and polysialylated neural cell adhesion molecule (NCAM), being expressed only in nonmyelinated axons [14].

The myelination done by a SC after its differentiation is closely linked both to its ability to synthesize a basal lamina and to its deposition. Furthermore, the presence of the axon and its intimate relationship with SC is extremely important, since it is in the axon that genes will be expressed then will maintain the myelinizing phenotype throughout the whole process [15], being the neurofascin gene an example, which plays an important role in the more advanced stages of myelination [14].

The axon also plays a key role in the activation through neuregulin of the ErbB2 and ErbB3 receptors of SCs, which are responsible for signaling the onset of the myelination process [16]. Therefore, the activation process occurs both through the inactivation of the signals that determine the immature state of SCs, and the activation of pro-myelin signals, which involve the transcription factors KROX20, octamer-binding transcription factor 6 (OCT6) and brain 2 class III POU domain protein (BRN2), NGFI-A-binding proteins 1 and 2 (NAB1/2), phosphatidylinositol 3-kinase (PI3K) signaling, and v-ski sarcoma viral oncogene homologue (SKI) [13].

4. Injuries to the peripheral nervous system

PNS axons can regenerate and recover their function after injury, fact that does not occur with CNS axons, which do not regenerate spontaneously [17]. However, there are some factors that contribute to an inefficient functional recovery, among which are (1) damage to the cell body of the neuron due to retrograde degeneration, making regeneration impossible; (2) nonviability of axonal growth due to nerve injury or subjacent diseases; (3) changes in the central circuits in which the injured neurons participate due to the plasticity of the neural connections; and (4) low specificity of reinnervation by the new axons, when the target organs are reinnervated by nerve fibers of different functions [18].

In peripheral neuropathic diseases, changes and symptoms vary depending of injured nerve type (motor, sensory, or autonomic) [19]. Hence, injury can lead to different levels of nerve fiber damage, including substantial functional loss, resulting in decreased quality of life due to permanent changes in motor and sensory functions, as well as secondary problems such as neuropathic pain [18]. As a result, several pathophysiological changes, including morphological and metabolic changes, that occur in the injured site and in the neuron body, in the proximal and distal segments [9].

These injuries are common, and their repair is still a problem in microsurgery. One method widely accepted by surgeons is to solve the problem with an autologous donor nerve, which

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is linked to some disadvantages, such as an extra incision to removal of a healthy sensory nerve, resulting in a sensory deficit [10]. On the other hand, in cases of chronic axotomy, the number of SCs in the distal stump decreases drastically, which makes the regeneration of axons difficult [20].

In this way, there are currently no repair techniques that ensure the recovery of normal sensory and motor functions after severe traumatic nervousness. Therefore, new therapeutic strategies are needed to potentiate axonal regeneration, promote selective reinnervation of the target, and modulate the central reorganization [18].

5. Wallerian degeneration

After nerve injury, the proximal fibers of the trauma are disconnected from the body of the neuron, resulting in a loss of muscles innervation, which leads to a total or partial loss of the motor, sensorial, and autonomic functions [18, 21]. In this way, a series of cellular alterations is initiated in the distal segment of the injured nerve, triggering the process of Wallerian degeneration, in which fragmentation and disintegration of the axons occur [17]. This disintegration is the result of a significant increase of Ca^{2+} in axoplasm, which is normally maintained at low concentrations in a healthy axon. On this way, Ca^{2+} sensitive protease (calpain) is activated, thereby degrading the axon cytoskeleton [22–24].

Wallerian degeneration also leads to removal and recycling of fragments derived from myelin rupture. For this, there is a recruitment of (1) macrophages, due to an increase in the permeability of blood-nerve-barrier (BNB) [24], contributing to removal of debris, phagocytizing them; and (2) SCs, which are dedifferentiated, divide and proliferate, also assisting in this removal and regulating factors that regulate Wallerian degeneration and nerve regeneration [12].

Besides that, several molecular changes are observed in the distal stump of the injured nerve, such as: (1) elevation of NGF messenger ribonucleic acid (mRNA) concentration, related to macrophage migration to the site and increased concentration of interleukin; (2) elevation of brain-derived neurotrophic factor (BDNF) mRNA concentration; (3) downregulation of NT-3 mRNA after nerve injury; (4) NT-4/5 mRNA decreases in the first hours after trauma but increases significantly after 2 weeks; (5) the expression of the transmembrane receptor for neurotrophic factors, p75NGFR, increases both in the distal stump and in the repair sites; (6) the expression of members of the tyrosine kinase family: trkA receptor is not detected, whereas the trkB and trkC levels in the SCs increase; (7) ciliary neutrophic factor (CNTF) mRNA decreases dramatically; and (8) rapid upregulation of glial cell line-derived neutrophic factor (GDNF) mRNA expression in SCs [25].

6. Peripheral nervous system regeneration

The main function of axonal regeneration is to replace the distal segment of the nerve that was lost during degeneration, allowing the reinnervation of peripheral segments and the restitution of their functions. Therefore, injured axons of peripheral nervous system are able to

regenerate and reinnerve their target organs [21]. In view of this, while the degeneration process is happening in distal stump of the axon, the proximal stump regeneration begins, which occurs through the retrograde reaction that leads to metabolic changes [21, 26].

Moreover, axonic and myelinic debris were previously removed from the distal part of the injured site during the process of Wallerian degeneration by macrophages and CSs [12, 17]. The relationship between axons and SCs is intense and essential for regeneration process [27], since it is necessary a permissive environment for it. This is provided by the set of (1) extracellular matrix, (2) extracellular matrix proteins (ECMs) or neurostimulatory peptides (LN-1 or fragments of LN-1), (3) neutrophic factors, and (4) the SCs themselves [28].

Furthermore, SCs lose their myelinizing phenotype, leaded by a decrease in type III neuregulin 1. They become dedifferentiated and increase the expression of the growth factor-promoting genes [22], which aid the expansion of newly formed growth cones on the regenerating fibers. In addition, they regulate extracellular matrix molecules [20]. Thus, to aid the expansion of the axon, SCs increase their synthesis of adhesion molecules (CAMs), such as N-CAM, Ng-CAM/L1, N-cadherin, and L2/HNK-1; secrete ECM proteins, such as laminin (LN), fibronectin (FN), heparan sulfate proteoglycans (HSP), and tenascin in the basal membrane; secrete several neurotrophic factors, such as NGF and BDNF, to attract the fibers during their regeneration, being captured in the growth cones, incorporated into axon, and transported to the body of the neuron; and, together with macrophages, express anti-inflammatory cytokines such as interleukin (IL)-10 (NGEOW), which inhibit the inflammatory process initiated in Wallerian degeneration [25, 27].

Then, in the beginning of regeneration, it is possible to observe an axonal shoot appearing in the distal stump, while the surface of the SCs guides the growth cone, allowing the beginning of myelination [10]. This directional guidance track that provides way for axon growth is called Büngner band, which is made up by SCs [24], by the basal membrane where the SCs are situated [19], as well as by connective tissue. If the distance to be covered by the new axon segment is short, there may be a reinnervation in a healthy muscle. However, if reinnervation is delayed, SCs degenerate and no longer promote axon growth. Thus, in addition to atrophy in target muscle, the receptivity to synapse formation is lost [22].

In view of the active participation of SCs in the regeneration of peripheral nerves, the use of these cells has enabled the development of new strategies for the treatment of peripheral nervous disorders [29], including demyelinating diseases and spinal cord injuries [11].

7. Nucleotids as elements with therapeutical properties

It is known that extracellular nucleotides are fundamental in the regulation of several cellular and pathological mechanisms, being important in the control of homeostasis [30–32]. The regulation of the increase of other substances in cells, glucose and urea metabolism, and participation in inflammatory response processes are among these mechanisms [33, 34].

Nucleotides are monomeric structural units composed by a sugar moiety, attached to one or more phosphate groups, and a nitrogenous base, which may be cytosine, adenine, guanine,

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thymine, or uracil [35]. They are present inside cells playing a key role in several processes, such as the regulation of programmed cell death, energy generation, and cellular signaling [36].

The intracellular or physiological function performed by nucleotides is related to the type of receptor which this binds [37]. These receptors, known as purinoreceptors, are divided into two types: P1, which are adenine selective receptors, and P2, which are subdivided into P2X receptors, formed by ionotropic receptors of adenosine triphosphate (ATP), and P2Y coupled to G proteins, selective for nucleotides containing adenine and/or uracil [38].

This signaling modulates processes such as endocrine and exocrine secretion, platelet aggregation, cell proliferation, differentiation, bone resorption, inflammation, and healing [36]. In addition, P2Y receptors are related to cell survival or death mechanisms in order to promote tissue healing and regeneration, an important process in pathological conditions [39].

Several types of nucleotides—such as ATP, UTP and adenosine—act in the nervous system as signaling molecules in innumerable processes, such as neurogenesis, migration, neuron differentiation, apoptosis, and glial cell proliferation [40]. They may play a specific role, assisting in the development of the nervous system and its regeneration, in addition to participating in synaptic transmission and neuromodulation [41, 42].

Both the ATP-1 and UTP-2 nucleotides are mostly intracellular. However, both can be secreted into the extracellular medium by various mechanisms. One of them is the cellular damage, which leads to the release of nucleotides by necrotic or apoptotic cells, thus constituting a danger signal. Other mechanisms are exocytosis and transport by vesicles and membrane channels [43].

8. Nucleotids and cobalamin and their application for regeneration

The presence of extracellular nucleotides in the nervous system as signaling and regulatory molecules in several processes has been recognized for presenting neuromodulatory function involved in several stages of metabolism [44] and because they are potent microglial stimulators in both normal and pathophysiological pathways [45].

P2Y receptor ligands have been shown to be positively regulated in spinal microglial cells following damage in peripheral innervation, contributing for example by aiding the treatment of neuropathic pain and stimulating the release of neurotrophic factor from the brain [46]. In addition, extracellular nucleotides are capable of interacting with proximal cells, inducing cell differentiation and neurite outgrowth in glial cells [39, 47, 48]. Thus, they are molecules that, when induced, are effective in the treatment of several peripheral neurological syndromes, such as peripheral neuropathy [49, 50].

Another important role that nucleotides play is in the mechanism of macrophages recruitment as well as in the production of interleukins—such as IL-6, IL-9, and IL-13—via activation of P2Y and mRNA receptors [51–53]. The recruitment of macrophages to the injured site is essential for the regeneration of nervous tissue, since it promotes a rapid production of myelin in the PNS, as well as formation of myelin associated with glycoproteins and, therefore, facilitates nerve regeneration [54].

The interleukins mentioned above are important mediators of nerve regeneration, which act via interleukin receptors [55]. Studies show that IL-6 is not detected in intact nerves; however, in injured nerves, it is increased and it is regulated by neurotrophic factors, which are released by SCs [56].

Drugs containing nucleotides are prescribed, for example, to patients with neuromuscular diseases and diabetic polyneuropathy, since their clinical efficacy has already been studied, and *in vivo* tests have demonstrated their role in accelerating the regeneration of nerves and muscles after the sciatic lesion [29]. Mechanisms of tissue restoration have a vital importance for regeneration of the PNS, and nucleotides can be used as treatment for these lesions, since they play an important role in nerve regeneration [57].

In vitro studies show that UTP has an important costimulatory role in the wound healing process, activating, and modulating growth factors, which confirms the role of extracellular nucleotides in the process of tissue regeneration [58]. UTP, through the activation of P2Y purinergic receptors, induces in the SCs an N-cadherin expression increase which is closely related to growth and orientation of axons, besides having an important role in cell adhesion and myelination [59].

Derivatives of cytidine have been shown to be beneficial against various pathologies of the central nervous system, as well as neurodegenerative diseases. It is able to promote the regeneration of nerves in the peripheral nervous tissue and promotes the functional recovery of these nerves. Preclinical studies have shown that it promotes nerve regeneration in murine models. In addition, cytidine administered alone or in combination has an effect on peripheral nerve regeneration in rats, which compounds are believed to have the same function as cytidine in the regeneration of peripheral nerves [60, 61].

Evidences have shown that the combination of CMP and UTP has a positive effect on tissue regeneration [29, 62], as well as a meta-analysis study showed that P2Y receptor ligands are a promising therapeutic strategy for the treatment of neuropathic pain in murine models [63]. A clinical study of 26 patients with optic neuropathy–administered cytidine diphosphate (CDP)-choline for about 6 months showed that CDP-choline is effective in regenerating optic nerves in these patients [64].

Nunes et al. compared the efficacy of uridine and cytidine nucleotides associated or not with hydroxycobalamin (**Figure 3**) in the treatment of signs and symptoms of anemia. They observed that the group treated with the three elements achieved better efficacy—corresponding to an improvement in laboratory assessments, weight gain, and decreased pain—than the group treated only with nucleotides [65]. Another study evaluated the use of the three therapeutic elements in the treatment of patients with alcoholic polyneuropathy, and it was observed that their use was safe and effective, with decreased pain and improved motor coordination [66].

Further study carried out by Negrão et al. tested the use of uridine nucleotides associated with vitamin B12 and folic acid to assess the clinical improvement of patients with peripheral neuropathy associated with neuropathic pain. They observed a significant improvement in pain intensity, number of affected areas, and pain irradiation, suggesting a possible reduction in the use of nonsteroidal anti-inflammatory drugs (NSAIDs) [49].

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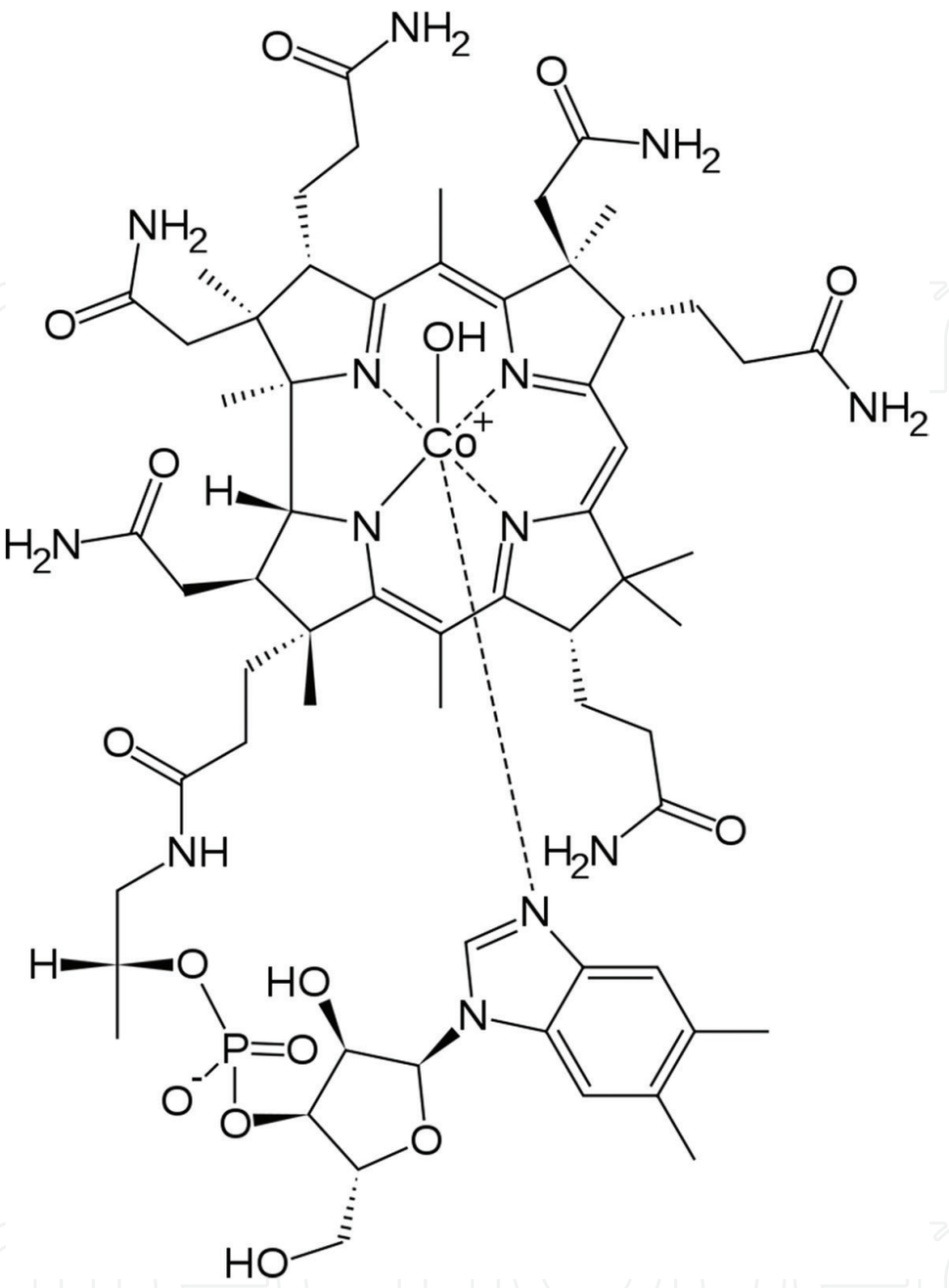

Figure 3. Molecular structure of cobalamin, Vitamin B12, whose central cobalt atom is attached to a hydroxyl radical.

Several meta-analysis studies have shown that there is a vitamin B12 deficiency in peripheral neuropathies due to type II diabetes, and that the administration of vitamin B12 in these patients is efficient as a treatment of neuropathy and neuropathic pain and may even be administered as prophylactic supplementation in this population [67–69].

Neurological disorders related to exposure of nitrous oxide anesthesia have been reported and are linked to toxicity in the spinal cord, since this substance causes irreversible oxidation of the cobalt ion present in the cobalamin structure [70]. In such cases, homocysteine methylation for S-adenosyl-methionine (SAM) formation is defective, leading to the formation of unstable

myelin basic proteins [71]. Also, clinical study has shown that parenteral administration of vitamin B12 in a series of cases with different neurological abnormalities, where patients had vitamin B12 deficiency were effective for the treatment of peripheral neurological damage [72–75].

Vitamin B12 plays an important role in DNA synthesis and neurological functions, and its deficiency induces a failure of the methylation of basic myelin proteins and may be the cause of myeloneuropathy or peripheral neuropathy [76]. Weir and Scott showed that B12 deficiency is very common in the elderly and is important in the brain where SAM synthesis occurs [77]. In addition, other pathophysiological conditions such as survivors of acute lymphoblastic leukemia during childhood, patients with rare Foster Kennedy syndrome, or patients with nitric oxide toxicity, may present neuropathy due to vitamin B12 deficiency, and in these cases, the administration of it is used as treatment [76–79].

Futhermore, it is known that vitamin B12 deficiency causes neurological changes that form a classic clinical picture of subacute degeneration of the dorsal and lateral vertebral column as a consequence of changes in myelin formation [80, 81] and in that cases, the standard treatment is the administration of cobalamin [82]. Besides, B vitamins have an analgesic effect in painful neuropathic and nociceptive syndromes [83].

9. Molecular perspectives

Endogenous substances when administered exogenously tend to be processed as elements belonging to normal physiology, in which homeostatic mechanisms act to bring them back to their normal levels [84, 85]. The control of blood levels of nucleosides is exerted by the balance between three different metabolic pathways: (1)—hepatic *de novo* synthesis, (2)—salvage pathway, (3)—hepatic degradation [86–88]. Both uridine and cytidine pass into the nervous system from the choroid plexus and the blood-brain barrier, through nucleoside transport systems [89].

These systems are divided into low-affinity equilibrium transport system (SLC29 family) and high-affinity concentration transport system, which is sodium-dependent, substrate-selective and unidirectional (SLC28 family) [90]. Both the transport of blood to the cerebral extracellular fluid and the extracellular cerebral fluid to the neural cells are mediated by these transporters [91, 92].

Oral administration of cytidine to humans rapidly elevates uridine serum levels because of the conversion of part of it into uridine [93]. Therefore, even if administration of exogenous cytidine leads to increased levels of its nucleoside in neural cells, since the uridine is the main precursor for CTP used in the synthesis of brain phosphatides [89] (see **Figure 4**).

The biosynthesis of phosphatidylcholine, the most abundant phospholipid in the brain and phosphatidylethanolamine proceeds through activation of the amine moiety (namely choline or ethanolamine) by coupling to CDP prior to its addition to the diacylglycerol, leading to the production of CDP-choline or CDP ethanolamine and inorganic phosphate [94]. Both cytidine and uridine are able to increase neuronal membrane synthesis through increasing levels of CTP [95–97].

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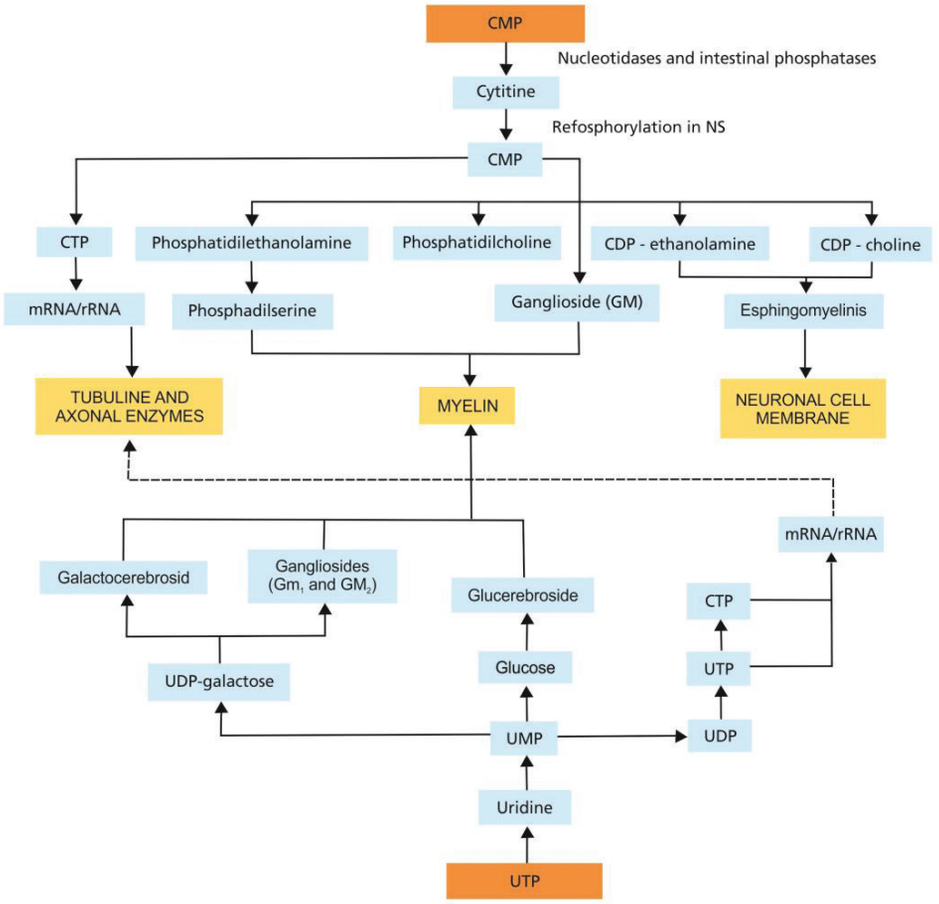

Figure 4. Overview of metabolic pathways (protein synthesis, myelin sheath synthesis, and neuronal cell membrane synthesis), to which exogenous nucleotides CMP and UTP integrate. Abbreviations: **CDP:** cytidine diphosphate; **CMP:** cytidine monophosphate; **CTP:** cytidine triphosphate; **mRNA:** messenger ribonucleic acid; **NS:** nervous system; **rRNA:** ribosomal ribonucleic acid; **UDP:** uridine diphosphate; **UMP:** uridine monophosphate; **UTP:** uridine triphosphate.

The circulating pyrimidines, in addition to being incorporated into nucleic acids, may serve as substrates for the salvage route of pyrimidine nucleotide synthesis, as precursors of cytidine triphosphate (CTP) [98] and as precursors for uridine diphosphate (UDP) and uridine triphosphate (UTP), which activate the brain's P2Y receptors [99].

Cytidine nucleotides are extremely important for the replacement of phospholipids that serve as substrates for cell membrane synthesis in the nervous system, such as phosphatidylinositol, phosphatidylcholine and phosphatidylethanolamine [89, 100]. In addition, they are also involved in the modulation of pain transmission by the activation of P2Y receptors [101].

Uridine nucleotides activate specific P2Y receptor subtypes in humans [102, 103], acting as cell-to-cell signaling in the nervous system [104, 105]. They are dependent on the activity of the axonal signals in neighboring oligodendrocytes and their structure consists of seven transmembrane domains, with the N-terminal domain in the extracellular space and the C-terminal domain in the cytoplasm [19, 106]. In addition, activation of P2Y receptors is usually associated with the stimulation of various mitogen-activated protein kinases (MAPKs), mainly the extracellular signal-regulated protein kinase 1/2 [38].

The activation of purinergic receptors in axons and SCs in regeneration processes is vital, since their inhibition leads to improper regeneration of the nerve [107]. Physiologically, extracellular UTP is capable of causing secretion in calcium chloride epithelial cells and in glial cells of catecholamines. In the SCs, UTP treatment contributes to the increase of the excitatory communication between axons and these cells through the secretion of ATP [19] and increased N-cadherin expression, an adhesion protein that could reanalyze the early contacts between cells and axons to accelerate myelination and axonal regeneration [59].

Subtypes of UTP-activated receptors P2Y2 and P2Y4 in humans are coupled to G_q protein [102] and are mainly involved in long-term effects, such as differentiation, neurite outgrowth, and cell survival or death [108, 109]. These receptors are normally activated during pathological conditions and participate in inflammatory processes of the nervous system [102], in which they trigger and sustain reactive astrogliosis, the reaction to brain trauma [104, 105], characterized by cellular proliferation and neural circuit remodeling [110].

The P2Y2 and P2Y4 receptors activate phospholipase C, increasing the cytosolic Ca^{2+} concentration from the intracellular reserves and the activation of protein kinase C in response to the production of inositol 1,4,5-trisphosphate and diacylglycerol, respectively [111]. Generally, P2Y receptors that increase intracellular Ca^{2+} concentration induce the tricarboxylic acid cycle and increase ATP production, which promotes the maintenance of ion homeostasis and antioxidant defense [109].

P2Y2 receptors are expressed by neurons, astrocytes, and microglia and regulate actin polymerization and cytoskeletal rearrangements through the Rac/Rho pathways [112], as well as the P2Y4 receptors [113]. Its activation confers neuroprotection in several ways: the promotion of neurite outgrowth, increased cell motility, nonamyloidogenic processing of the amyloid precursor protein, and increased phagocytosis and degradation of the amyloid-beta peptide [102, 111]. Moreover, studies have shown that microglia respond rapidly to nerve lesions by migrating to the spinal projection territories of the central terminals of injured primary afferents, with subsequent proliferation, activation of p38 MAPK and ERK1/2, and production of proinflammatory cytokines and chemokines [114].

UTP also participates in neuromodulation. The modulation exerted by activation of P2Y4 receptors is linked to the positive influence on excitatory transmission mediated by postsynaptic N-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, through increased glutamate release [111], while P2Y2 receptors modulation is linked to increased currents through the Ca^{2+} permeable transient receptors potential vanoloyide 1 (TRPV1) in the PNS [115]. This high concentration of intracellular Ca^{2+} can participate in responses through annexins—responsible for signal transduction, trafficking, and vesicle aggregation and membrane organization—that bind negatively charged phospholipids in a Ca^{2+}-dependent way [116].

In addition to UTP, other uridine derivatives also activate P2Y receptors, such as UDP, which activate the subfamily of P2Y6 and P2Y14 receptors [117, 118]. However, while P2Y6 receptors are coupled to G_q/11 protein, P2Y14 receptors are coupled to G protein, and the increase in their expression is also related to the occurrence of peripheral nerve lesions, being regulated

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by p38 MAPK [114]. The activation of the P2Y6 receptors in microglia cells causes a rapid change in their morphology, with phagocytosis of damaged neurons being increased, through the reorganization of actin by a pathway mediated by the activation of protein kinase C (PKC) and PCL linked to the increase of intracellular Ca^{2+} [94].

Cobalamin and its analogs act on the nervous system promoting neurite outgrowth and neuronal survival. It plays the role of coenzyme in the methylation of homocysteine by methionine synthase to form methionine, in isomerization of 1-methylmalonyl-CoA in succinyl-CoA catalyzed by 1-methylmalonyl-coenzyme A mutase [119, 120], and in the activation of Erk1/2 and Akt [8].

In addition to the formation of methionine from homocysteine, methionine synthase is required for the synthesis of S-Adenosyl-methionine [121, 122]. SAM is a key metabolite in amino acid transmethylation responsible for the biological methylations that modify nucleic acids, fatty acids, porphyrins, phospholipids, polysaccharides, biogenic amines, and proteins, such as myelin basic protein (MBP), one of the proteins responsible for the compaction of the cytoplasmic surfaces of the myelin sheath [123, 124].

Vitamin B12, as the effector of methionine synthase, plays a key role in ensuring the integrity and stability of the myelin basic protein, since it depends on the methylation of one of its amino acids. A deficiency in this methylation can lead to poor protein formation and instability [119]. In addition, methionine also facilitates the formation of formyl tetrahydrofolate (formyl THF) and tetrahydrofolate (THF), which are involved in the synthesis of purines [125].

Under normal conditions, when the folding and/or trafficking of a polypeptide fails, the protein is targeted for degradation by the ubiquitin-proteasome system. However, when there is a pathologic condition, there is interruption of the balance between the synthesis/folding and degradation pathways, and the accumulation and aggregation of proteins are favored, which are a characteristic of several neurodegenerative diseases [126].

10. Discussion

Some clinical studies using nucleotides and vitamin B12 for the treatment of diseases of the peripheral nervous system have been carried out, proving that CMP, UTP, and hydroxycobalamin are effective and can be used safely for this purpose. The studies cited below are summarized in **Table 1**.

Lauretti et al. evaluated the efficacy of oral administration of the cytidine-uridine-hydroxycobalamin complex in the treatment of chronic neuropathic lower back pain. The study evaluated 48 adult patients, aged 21–80 years, with a history of pain after 6 months, whose previous traditional treatments were ineffective. During the course of treatment, patients were given oral fluoxetine (20 mg/day) daily and were divided into two groups: the control group, which received a combination of 40-mg lidocaine, 30-mg clonidine, and 10-mg dexamethasone, diluted with physiological solution; and study group where a tablet containing

Authors	Type of study	Sample	Objectives/methods	Results/conclusion
Parisi et al. [64]	Clinical study of the effects of CDP-choline on patients with optic neuropathy	26 patients were treated with the disease and compared with 14 normal individuals	Patients were treated with oral CDP-choline for two 60-day periods and one later to complete 360 days of study initiation. The results were evaluated by electrophysiological exams.	There was a significant improvement with the treatment of CDP-choline patients
Nunes et al. [66]	Clinical study of the use of CMP UTP and B12 to treat alcoholic polyneuropathy	120 patients between 18 and 65 years of age were evaluated	Patients with alcoholic neuropathy were treated with CMP, UTP and B12 intramuscularly in 6 days and orally for 30 days and then the effects were monitored	The combination of uridine, cytidine, and vitamin B12 was safe and effective in the treatment of patients with alcoholic neuropathy
Mibielli et al. [7]	The analgesic effects of the combination UTP, CMP and hydroxycobalamin were evaluated in a self-paired evolutionary model	17 men and 24 women were treated	Analysis of previously unpublished data from investigators files on VAS and PFQ pain scores of the group of patients treated with the combination of UTP, CMP and hydroxycobalamin	The combination of UTP, CMP and hydroxycobalamin seems to have analgesic properties in the medium term
Negrão et al. [49]	Clinical evaluation of patients with peripheral neuropathy and neuropathic pain	212 patients with a mean age of 59 (±14.4) years of age	Patients received daily treatment of uridine monophosphate + folic acid + vitamin B12 for 2 months in conjunction with anti-inflammatories and were evaluated using a pain-detection questionnaire	The combination of UMP + vitamin B12 + folic acid is effective against neuropathic pain associated with peripheral neuropathy. The use of anti-inflammatory decreased by more than 70%.
Negrão and Nunes [50]	Observational study of patients with neuropathy	48 patients were evaluated	Patients received daily treatment of uridine monophosphate + folic acid + vitamin B12 for 2 months in conjunction with analgesics and anti-inflammatories, and were evaluated using a pain-detection questionnaire	Uridine monophosphate + folic acid + vitamin B12 reduced total pain score, intensity and characterization of pain and associated symptoms and the use of analgesic and anti-inflammatory drugs reduced in 77.4%

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Authors	Type of study	Sample	Objectives/methods	Results/conclusion
Solomon [68]	A clinical study that measured the amount of B12 in cancer patients associating neuropathy and neuropathic pain with B12 deficiency and consequent increase in malignancy	241 patients were evaluated	We evaluated the levels of B12 and malignancy in individuals with cancer during a period of 4 years in a cancer study center	B12 therapy plays an important role in the prevention of neuropathy and neuropathic pain that are generally encountered during cancer malignancy advances

Table 1. Summarized clinical studies using nucleotides and vitamin B12 for the treatment of diseases of the peripheral nervous system.

the cytidine-uridine-hydroxycobalamin complex was added and given orally every 12 hours. The results of the study indicated that the co-administration of the complex during treatment led to a decrease in the intensity of chronic neuropathic low back pain and a reduction in the consumption of rescue analgesics, improving and enhancing the quality of treatment in patients with neuropathic low back injuries [6].

Parisi and colleagues used CDP choline to treat optic neuropathy in a study with 26 sick patients in the test group and 14 healthy subjects in the control group. The treatment was done orally for two 60-day periods and a later period until it was completed 360 days after the start of the study. The results were evaluated through electrophysiological examinations, leading to a significant improvement in the patients. Thus, it has been found that CDP choline can be used to treat patients with optic neuropathy [64].

Goldberg and colleagues evaluated the use of a combination of uridine triphosphate (UTP), cytidine monophosphate (CMP), and hydroxocobalamin in a double-blind, randomized study in the treatment of neuralgia due to degenerative orthopedic alterations with neural compression. The patients were divided into two groups, being Group A: total daily dose of 9 mg UTP, 15 mg CMP, 6 mg hydroxycobalamin; and Group B: total daily dose of 6 mg hydroxocobalamin. At the end of the 30-day treatment period, there were reductions in the pain scale scores in both groups; however, there was a significantly larger reduction in the scores of the Group A patients. Based on these findings, the authors concluded that the combination of UTP, CMP, and vitamin B12 has a positive effect on pain and functionality improvement in the treatment of degenerative orthopedic alterations with neural compression [127].

Nunes and collaborators administered CMP, UTP, and hydroxycobalamin in patients with alcoholic polyneuropathy, a disorder in the peripheral nervous system involving motor, sensorial, and autonomic nerves. This study included 120 patients aged 28–65 years, who were treated with doses intramuscularly for 6 days and orally for 30 days. Afterward, the efficacy of the treatment was evaluated through sensorial motor tests as well as a visual evaluation of pain. With this, it was concluded that the treatment was effective and safe, reducing pain and improving the motor activity of the patients [66].

Negrão et al. performed an observational clinical study of 212 patients with peripheral neuropathy and neuropathic pain, treated orally for 2 months with capsules of uridine monophosphate (UMP), folic acid, and hydroxycobalamin. These patients had a mean age of 59 years. The results were evaluated using a questionnaire, where the patient reveals to the doctor the areas of the body that present pain. The result showed that the treatment was effective, and the statistical analysis showed that there was improvement not only of the overall picture but also factors such as intensity of pain and affected areas decreased with treatment. In addition, patients greatly reduced the adjunctive use of analgesic or anti-inflammatory drugs [49].

In another study, the same group of researchers treated 48 patients with neuropathy or neuropathic pain over a two-month period. Patient evaluations showed a reduction in intensity and areas affected by pain, showing the efficacy of the treatment and confirming the results of the previous study. As in the previous study, the treatment induced improvement of the patients allowing the reduction of analgesic or anti-inflammatory use by up to 70% [50].

Mibielli et al. conducted a clinical study to evaluate the analgesic effects of UTP, CMP, and hydroxycobalamin in the treatment of peripheral pain. A total of 17 men and 24 women with a mean age of 49 years were treated with oral administration of the compound. The evaluation of the results was performed with a pain questionnaire. The study showed that this compound presents analgesic and neuroregenerative properties in the medium term, as well as indicated subsequent randomized clinical trials to confirm the results [7].

The increase in the malignancy of some types of cancer is associated with the appearance of peripheral neuropathies. A recent study evaluated, over 2 years, levels of vitamin B12 in cancer patients at a cancer study center. From the analyses made, it was verified that vitamin B12 deficiency is associated with the appearance of neuropathies and peripheral pain. Therefore, treatment with vitamin B12 may prevent cancer patients from developing neuropathies or neuropathic pain [68].

11. Conclusion

New therapeutic strategies are needed to potentiate regeneration in nerve injuries, and the use of Schwann cells has enabled the development of new strategies for the treatment of peripheral nervous disorders. Numerous studies have been done with the aim of finding new targets and new drugs, and the use of uridine and cytidine nucleotides associated with hydroxocobalamin has proven to be very effective.

It can be assumed that the nucleotide supplementation of cytidine and uridine associated with vitamin B12 in situations of neural structural regeneration can increase its availability in SCs, aiding in neuro-regeneration. Therefore, it is a set of drugs that can be used safely in the treatment of neuropathies and other diseases associated with degeneration of the peripheral nervous system.

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Abbreviations

AMPA	α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
ATP	Adenosine triphosphate
BDNF	Brain-derived neurotrophic factor
BNB	Blood-nerve-barrier
CAM	Cell adhesion molecule
CDP	Cytidine diphosphate
CMP	Cytidine monophosphate
CNS	Central nervous system
CNTF	Ciliary neutrophic factor
CTP	Cytidine triphosphate
D	Day
DNA	Deoxyribonucleic acid
ECMs	Extracellular matrix
ERK	Extracellular signal-regulated kinase
FN	Fibronectin
GDNF	Glial cell line-derived neutrophic factor
IL	Interleukin
LN	Laminin
M	Month
MAPKs	Mitogen-activated protein kinase
MBP	Myelin basic protein
NGF	Nerve growth factor
NMDA	N-methyl-D-aspartate
NSAIDs	Nonsteroidal antiinflammatory drugs
NT	Neurotrophin
OCT6	Octamerbinding transcription factor 6
PI	Phosphatidylinositol
PKC	Protein kinase C
PLC	Phospholipase C
PNS	Peripheral nervous system
RNA	Ribonucleic acid
SAM	S-adenosyl-methionine

SCs	Schwann cells
THF	Tetrahydrofolate
Trk	Tyrosine kinase family
TRPV1	Transient receptor potential vanoloyide 1
UDP	Uridine diphosphate
UMP	Uridine monophosphate
UTP	Uridine triphosphate
V	Visit
VAS	Visual analogic scale

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References

[1] Woolf CJ. Neuropathic pain. In: Pain. Philadelphia: Lippincott Williams Wilkins, 2004: 765–95.

[2] Silva GNS, Monteiro PB, Virgínio NA, Souto CGV, Oliveira MVAV. Systematization of nursing care for patients with Herniated Disc. Health Science Magazine New Hope. 2013;11(2):55–71.

[3] Serra JP, Veciana MG, Bordas LB. Therapeutic effects of an association of C.M.P., U.T.P., and vitamin B12 in fifty cases of peripheral neuropathies. New England Journal of Medicine (Sp Ed). Mayo 1972;VI(64):1–7.

[4] Gallai V, Mazzotta G, Montesi S, Sarchielli P, et al. Effects of uridine in the treatment of diabetic neuropathy: an electrophysiological study. Acta Neurologica Scandinavica. 1992;86:3–7.

[5] Muller D. Treatment of neuropathic pain syndrome. Results of an open study on the efficacy of a pyrimidine nucleotide preparation. Fortschritte der Medizin Originalien. 2002;120:131–3.

[6] Lauretti GC, Omals M, Pereira AC, et al. Clinical evaluation of the analgesic effect of the cytidine-uridine-hydroxocobalamin complex as a coadjuvant in the treatment of chronic neuropathic low back pain. Column. 2004;3(2):73–6.

[7] Mibielli MA, Nunes CP, Scussel AB, Suchmacher Neto M, Oliveira L, Geller M. Symptomatic improvement in an acute, non-traumatic spine pain model with a combination of uridine triphosphate, cytidine monophosphate, and hydroxocobalamin. Pain Studies and Treatment. 2014;v. 02, pp. 6–10.

[8] Okada K, Tanaka H, Temporin K, Okamoto M, Kuroda Y, Moritomo H, et al. Methylcobalamin increases Erk1/2 and Akt activities through the methylation cycle and promotes nerve regeneration in a rat sciatic nerve injury model. Experimental Neurology. 2010;222(2):191–203.

[9] Geuna S, Raimondo S, Ronchi G, Di Scipio F, Tos P, Czaja K, Fornaro M. Histology of the peripheral nerve and changes occurring during nerve regeneration. International Review of Neurobiology. 2009;87:27–46.

[10] Johnson EO, Zoubos AB, Soucacos PN. Regeneration and repair of peripheral nerves. Injury. 2005;36(4):S24–9.

[11] Bhatheja K, Field J. Schwann cells: origins and role in axonal maintenance and regeneration. The International Journal of Biochemistry & Cell Biology. 2006;38(12):1995–9.

[12] Campana WM. Schwann cells: activated peripheral glia and their role in neuropathic pain. Brain, Behavior, and Immunity. 2007;21(5):522–7.

[13] Jessen KR, Mirsky R. The origin and development of glial cells in peripheral nerves. Nature Reviews. Neuroscience. 2005;6(9):671–82.

[14] Sherman DL, Brophy PJ. Mechanisms of axon ensheathment and myelin growth. Nature Reviews. Neuroscience. 2005;6(9):683–90.

[15] Garbay B, Heapec AM, Sargueila F, Cassagne C. Myelin synthesis in the peripheral nervous system. Progress in Neurobiology. 2000;61(3):267–304.

[16] Pereira JA, Baumann R, Norrmén C, Somandin C, Miehe M, Jacob C, Lühmann T, Manten N, Meijer D, Suter U. Dicer in Schwann cells is required for myelination and axonal integrity. Journal of Neuroscience. 2010;30(19):6763–75.

[17] Huebner EA, Strittmatter SM. Axon regeneration in the peripheral and central nervous systems. In: Cell Biology of the Axon. 2009. Springer Berlin Heidelberg:305–60.

[18] Navarro X. Neural plasticity after nerve injury and regeneration. International Review of Neurobiology. 2009;87:483–505.

[19] Canales TM. Study of the drug CMP Forte and nucleotide UTP in Schwann cells [thesis]. Barcelona: International University of Catalonia; 2011.

[20] Jonsson S, Wiberg R, McGrath AM, Novikov LN, Wiberg M, Novikova LN, Kingham PJ. Effect of delayed peripheral nerve repair on nerve regeneration, Schwann cell function and target muscle recovery. PloS One. 2013;8(2):e56484.

[21] Allodi I, Udina E, Navarro X. Specificity of peripheral nerve regeneration: interactions at the axon level. Progress in Neurobiology. 2012;98(1):16–37.

[22] Scheib J, Höke A. Advances in peripheral nerve regeneration. Nature Reviews. Neurology. 2013;9(12):668–76. DOI: 10.1038/nrneurol.2013.227.

[23] Gaudet AD, Popovich PG, Ramer MS. Wallerian degeneration: gaining perspective on inflammatory events after peripheral nerve injury. Journal of Neuroinflammation. 2011;8(1):110.

[24] Ngeow WC. Scar less: a review of methods of scar reduction at sites of peripheral nerve repair. Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology. 2010;109(3):357–66.

[25] Frostick, SP, Qi Yin, Kemp GJ. Schwann cells, neurotrophic factors, and peripheral nerve regeneration. Microsurgery. 1998;18(7):397–405.

[26] Zu-Lin C, Yu W-M, Strickland S. Peripheral regeneration. Annual Review of Neuroscience. 2007;30:209–33.

[27] Webber C, Zochodne D. The nerve regenerative microenvironment: early behavior and partnership of axons and Schwann cells. Experimental Neurology. 2010;223(1):51–9.

[28] Bellamkonda RV. Peripheral nerve regeneration: an opinion on channels, scaffolds and anisotropy. Biomaterials. 2006;27(19):3515–8.

[29] Martiáñez T, Carrascal M, Lamarca A, Segura M, Durany N, Masgrau R, Abian J, Gella A. UTP affects the Schwannoma cell line proteome through P2Y receptors leading to cytoskeletal reorganisation. Proteomics. 2012;12(1):145–56.

[30] Baer HP, Drummond GI. Physiological and regulatory functions of adenosine and adenine nucleotides. 1979. Raven Press.

[31] Rudolph FB. The biochemistry and physiology of nucleotides. The Journal of Nutrition. 1994;124(1 Suppl):124S–7.

[32] Corriden R, Insel PA. New insights regarding the regulation of chemotaxis by nucleotides, adenosine, and their receptors. Purinergic Signalling. 2012;8(3):587–98.

[33] Fausther M, Sévigny J. Nucleosides and extracellular nucleotides regulate hepatic functions through a complex system of membrane proteins. Biological Complications. 2011;334(2):100–17.

[34] Zimmermann H. Extracellular ATP and other nucleotides—ubiquitous triggers of intercellular messenger release. Purinergic Signalling. 2016;12(1):25–57.

[35] Florian J, Leszczyński J. Spontaneous DNA mutations induced by proton transfer in the guanine. Cytosine base pairs: an energetic perspective. Journal of the American Chemical Society. 1996;118(12):3010–7.

[36] Burnstock G. Pathophysiology and therapeutic potential of purinergic signaling. Pharmacological Reviews. 2006;58(1):58–86.

[37] Jacobson KA, Paoletta S, Katritch V, Wu B, Gao Z-G, Zhao Q, et al. Nucleotides acting at P2Y receptors: connecting structure and function. Molecular Pharmacology. 2015;88(2):220–30.

[38] Burnstock G. Purine and pyrimidine receptors. Cellular and Molecular Life Sciences. 2007;64(12):1471–83.

[39] Mamedova LK, Gao ZG, Jacobson KA. Regulation of death and survival in astrocytes by ADP activating P2Y 1 and P2Y 12 receptors. Biochemical Pharmacology. 2006;72(8):1031–41.

[40] Ulrich H, Abbracchio MP, Burnstock G. Extrinsic purinergic regulation of neural stem/progenitor cells: implications for CNS development and repair. Stem Cell Reviews and Reports. 2012;8(3):755–67.

[41] Neary JT, Zimmermann H. Trophic functions of nucleotides in the central nervous system. Trends in Neurosciences. 2009;32(4):189–98.

[42] Zimmermann H, Braun N. Extracellular metabolism of nucleotides in the nervous system. Journal of Autonomic Pharmacology. 1996;16(6):397–400.

[43] Jacobson KA, Boeynaems JM. P2Y nucleotide receptors: promise of therapeutic applications. Drug Discovery Today. 2010;15(13):570–8.

[44] Ipata PL. Origin, utilization, and recycling of nucleosides in the central nervous system. Advances in Physiology Education. 2011;35(4):342–6.

[45] Inoue K. The function of microglia through purinergic receptors: neuropathic pain and cytokine release. Pharmacology & Therapeutics. 2006;109(1):210–26.

[46] Tozaki-Saitoh H, Tsuda M, Miyata H, Ueda K, Kohsaka S, Inoue K. P2Y12 receptors in spinal microglia are required for neuropathic pain after peripheral nerve injury. Journal of Neuroscience. 2008;28(19):4949–56.

[47] Guarnieri S, Pilla R, Morabito C, Sacchetti S, Mancinelli R, Fanò G, Mariggiò MA. Extracellular guanosine and GTP promote expression of differentiation markers and induce S-phase cell-cycle arrest in human SH-SY5Y neuroblastoma cells. International Journal of Developmental Neuroscience. 2009;27(2):135–47.

[48] Menéndez-Méndez A, Díaz-Hernández JI, Miras-Portugal MT. The vesicular nucleotide transporter (VNUT) is involved in the extracellular ATP effect on neuronal differentiation. Purinergic Signalling. 2015;11(2):239–49.

[49] Negrão L, Almeida P, Alcino S, Duro H, Libório T, Melo SU, Figueira R, Gonçalves S, Neto PL. Effect of the combination of uridine nucleotides, folic acid and vitamin B12 on the clinical expression of peripheral neuropathies. Pain management. 2014;4(3):191–6.

[50] Negrão L, Nunes P. Uridine monophosphate, folic acid and vitamin B12 in patients with symptomatic peripheral entrapment neuropathies. Pain. 2016;6(1):25–9.

[51] Kobayashi D, Ohkubo S, Nakahata N. Contribution of extracellular signal-regulated kinase to UTP-induced interleukin-6 biosynthesis in HaCaT keratinocytes. Journal of Pharmacological Sciences. 2006;102(4):368–76.

[52] Endo Y, Isono K, Kondo M, Tamaoki J, Nagai A. Interleukin-9 and Interleukin-13 augment UTP-induced Cl ion transport via hCLCA1 expression in a human bronchial epithelial cell line. Clinical & Experimental Allergy. 2007;37(2):219–24.

[53] Zhang Z, Wang Z, Ren H, Yue M, Huang K, Gu H, Liu M, Du B, Qian M. P2Y6 agonist uridine 5′-diphosphate promotes host defense against bacterial infection via monocyte chemoattractant protein-1–mediated monocytes/macrophages recruitment. The Journal of Immunology. 2011;186(9):5376–87.

[54] Stoll G, Jander S, Myers RR. Degenerarion and regeneration os the peripheral nervous system: from Augustus Waller's observations to neuroinflammation. Journal of the Pheripheral Nervous System. 2002;7(1):13–27.

[55] Leibinger M, Müller A, Gobrecht P, Diekmann H, Andreadaki A, Fischer D. Interleukin-6 contributes to CNS axon regeneration upon inflammatory stimulation. Cell Death & Disease. 2013;4(4):e609.

[56] Hirota H, Kiyama H, Kishimoto T, Taga T. Accelerated nerve regeneration in mice by upregulated expression of interleukin (IL) 6 and IL-6 receptor after trauma. Journal of Experimental Medicine. 1996;183(6):2627–34.

[57] Rochkind S, Rousso M, Nissan M, Villarreal M, Barr-Nea L, Rees DG. Systemic effects of low-power laser irradiation on the peripheral and central nervous system, cutaneous wounds, and burns. Lasers in Surgery and Medicine. 1989;9(2):174–82.

[58] Boucher I, Kehasse A, Marcincin M, Rich C, Rahimi N, Trinkaus-Randall V. Distinct activation of epidermal growth factor receptor by UTP contributes to epithelial cell wound repair. The American Journal of Pathology. 2011;178(3):1092–105.

[59] Martiáñez T, Lamarca A, Casals N, Gella A. N-cadherin expression is regulated by UTP in schwannoma cells. Purinergic Signalling. 2013;9(2):259–70.

[60] Aslan E, Kocaeli H, Bekar A, Tolunay S, Ulus IH. CDP-choline and its endogenous metabolites, cytidine and choline, promote the nerve regeneration and improve the functional recovery of injured rat sciatic nerves. Neurological Research. 2011;33(7):766–73.

[61] Caner B, Kafa MI, Bekar A, Kurt MA, Karli N, Cansev M, Ulus IH. Intraperitoneal administration of CDP-choline or a combination of cytidine plus choline improves nerve regeneration and functional recovery in a rat model of sciatic nerve injury. Neurological Research. 2012;34(3):238–45.

[62] Pillois X, Chaulet H, Belloc I, Dupuch F, Desgranges C, Gadeau AP. Nucleotide receptors involved in UTP-induced rat arterial smooth muscle cell migration. Circulation Research. 2002;90(6):678–81.

[63] Ando RD, Mehesz B, Gyires K, Illes P, Sperlagh B. A comparative analysis of the activity of ligands acting at P2X and P2Y receptor subtypes in models of neuropathic, acute and inflammatory pain. British Journal of Pharmacology. 2010;159(5):1106–17.

[64] Parisi V, Coppola G, Ziccardi L, Gallinaro G, Falsini B. Cytidine-5′-diphosphocholine (Citicoline): a pilot study in patients with non-arteritic ischaemic optic neuropathy. European Journal of Neurology. 2008;15(5):465–74.

[65] Nunes CP, Higashi R, Ribeiro MG, de Souza Fonseca A, Leite A, Krymchantowski AV, et al. Efficacy and tolerability of a combination of uridine, cytidine, and vitamin B12 in anemia. A double-blind, comparative study versus nucleotide monotherapy. Revista Brasileira de Medicina. 2008;65(1/2):15.

[66] Nunes CP, Scussel Jr AB, Goldberg H, Goldwasser G, Oliveira L, Rzetelna H, et al. Alcoholic polyneuropathy: clinical assessment of treatment outcomes following therapy with nucleotides and vitamin B12. Research in Neurology: An International Journal. 2013;2013:g1–16.

[67] Roy RP, Ghosh K, Ghosh M, Acharyya A, Bhattacharya A, Pal M, Chakraborty S, Sengupta N. Study of vitamin B12 deficiency and peripheral neuropathy in metformin-treated early type 2 diabetes mellitus. Indian Journal of Endocrinology and Metabolism. 2016;20(5):631.

[68] Solomon LR. Functional vitamin B12 deficiency in advanced malignancy: implications for the management of neuropathy and neuropathic pain. Supportive Care in Cancer. 2016a;24(8):3489–94.

[69] Wang D, Zhai JX, Liu DW. Serum folate, vitamin B12 levels and diabetic peripheral neuropathy in type 2 diabetes: a meta-analysis. Molecular and Cellular Endocrinology. 2017. 163(3), 362–364.

[70] Aubart FC, Sedel F, Vicart S, Lyon-Caen O, & Fontaine, B. Neurological disorders due to vitamin B12 deficiency triggered by nitrous oxide. Neurological Review, 2007;163(3):362–4.

[71] Sakly G, Hellara O, Trabelsi A, & Dogui M. Reversible peripheral neuropathy related to vitamin B12 deficiency. Neurophysiologie Clinique/Clinical Neurophysiology. 2005;35(5):149–53.

[72] McCaddon A, Regland B, Hudson P, Davies G. Functional vitamin B12 deficiency and Alzheimer disease. Neurology. 2002;58(9):1395–9.

[73] Solomon LR. Vitamin B12-responsive neuropathies: a case series. Nutritional Neuroscience. 2016b;19(4):162–8.

[74] Roy S, Sable P, Khaire A, Randhir K, Kale A, Joshi S. Effect of maternal micronutrients (folic acid and vitamin B12) and omega 3 fatty acids on indices of brain oxidative stress in the offspring. Brain and Development. 2014;36(3):219–27.

[75] Guest J, Bilgin A, Hokin B, Mori TA, Croft KD, Grant R. Novel relationships between B12, folate and markers of inflammation, oxidative stress and NAD (H) levels, systemically and in the CNS of a healthy human cohort. Nutritional Neuroscience. 2015;18(8): 355–64.

[76] Petramfar P, Hosseinzadeh F, Mohammadi SS. Pseudo-Foster Kennedy Syndrome as a Rare Presentation of Vitamin B12 Deficiency. Iranian Red Crescent Medical Journal. 2016;18(6):e24610.

[77] Weir DG, Scott JM. Brain function in the elderly: role of vitamin B12 and folate. British Medical Bulletin. 1999;55(3):669–82.

[78] Jain P, Gulati S, Toteja GS, Bakhshi S, Seth R, Pandey RM. Serum alpha tocopherol, vitamin B12, and folate levels in childhood acute lymphoblastic leukemia survivors with and without neuropathy. Journal of Child Neurology. 2015;30(6):786–8.

[79] Morris N, Lynch K, Greenberg SA. Severe motor neuropathy or neuronopathy due to nitrous oxide toxicity after correction of vitamin B12 deficiency. Muscle & Nerve. 2015;51(4):614–6.

[80] Flippo TS, Holder WD. Neurologic degeneration associated with nitrous oxide anesthesia in patients with vitamin B12 deficiency. Archives of Surgery. 1993;128(12):1391–5.

[81] Stabler SP. Vitamin B12 deficiency. New England Journal of Medicine. 2013;368(2):149–60.

[82] Butler, CC, Vidal-Alaball, J, Cannings-John, R, McCaddon, A, Hood, K, Papaioannou, A, … & Goringe, A. Oral vitamin B12 versus intramuscular vitamin B12 for vitamin B12 deficiency: a systematic review of randomized controlled trials. Family Practice. 2006;23(3):279–85.

[83] Gazoni FM, Malezan WR, Santos FC. B complex vitamins for analgesic therapy. Revista Dor. 2016;17(1):52–6.

[84] Dissanayake S. Assessing the bioequivalence of analogues of endogenous substances ('endogenous drugs'): considerations to optimize study design. British Journal of Clinical Pharmacology. 2010;69(3):238–44.

[85] Marzo A. Pharmacokinetics of endogenous substances. Bollettino Chimico Farmaceutico. 1992;131(5):181–4.

[86] Gasser T, Moyer JD, Handschumacher RE. Novel single-pass exchange of circulating uridine in rat liver. Science. 1981;213(4509):777–8.

[87] Monks A, Cysyk RL. Uridine regulation by the isolated rat liver: perfusion with an artificial oxygen carrier. American Journal of Physiology—Regulatory, Integrative and Comparative Physiology. 1982;242(5):R465–70.

[88] Pizzorno G, Cao D, Leffert JJ, Russell RL, Zhang D, Handschumacher RE. Homeostatic control of uridine and the role of uridine phosphorylase: a biological and clinical update. Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease. 2002;1587(2):133–44.

[89] Cansev M. Uridine and cytidine in the brain: their transport and utilization. Brain Research Reviews. 2006;52(2):389–97.

[90] Pastor-Anglada M, Felipe A, Casado FJ. Transport and mode of action of nucleoside derivatives used in chemical and antiviral therapies. Trends in Pharmacological Sciences. 1998;19(10):424–30.

[91] Lu H, Chen C, Klaassen C. Tissue distribution of concentrative and equilibrative nucleoside transporters in male and female rats and mice. Drug Metabolism and Disposition. 2004;32(12):1455–61.

[92] Redzic ZB, Biringer J, Barnes K, Baldwin SA, Alâ€ Sarraf H, Nicola PA, et al. Polarized distribution of nucleoside transporters in rat brain endothelial and choroid plexus epithelial cells. Journal of Neurochemistry. 2005;94(5):1420–6.

[93] Wurtman RJ, Regan M, Ulus I, Yu L. Effect of oral CDP-choline on plasma choline and uridine levels in humans. Biochemical Pharmacology. 2000;60(7):989–92.

[94] Lecca D, and Stefania C. Uracil nucleotides: from metabolic intermediates to neuroprotection and neuroinflammation. Biochemical Pharmacology. 2008;7510:1869–81.

[95] Wang, L, Pooler, AM, Albrecht, MA, & Wurtman, RJ. Dietary uridine-5′-monophosphate supplementation increases potassium-evoked dopamine release and promotes neurite outgrowth in aged rats. Journal of Molecular Neuroscience. (2005);27(1):137–45.

[96] Cansev M, and Wurtman RJ. Exogenous cytidine-5′-diphosphocholine increases brain cytidine-5′-diphosphocholine levels in gerbils. Journal of Neurochemistry. 2005;94:105–6.

[97] Savci, V, and Wurtman RJ. Effect of cytidine on membrane phospholipid synthesis in rat striatal slices. Journal of Neurochemistry. 1995;641:378–84.

[98] Kennedy EP, Weiss SB. The function of cytidine coenzymes in the biosynthesis of phospholipides. Journal of Biological Chemistry. 1956;222(1):193–214.

[99] Von Kügelgen I. Pharmacological profiles of cloned mammalian P2Y-receptor subtypes. Pharmacology & Therapeutics. 2006;110(3):415–32.

[100] Bevilacqua J, Downes C, Lowenstein P. Visualization of agonist-stimulated inositol phospholipid turnover in individual neurons of the rat cerebral cortex and hippocampus. Neuroscience. 1994;60(4):945–58.

[101] Park SY, Im Kim H, Shin YK, Lee CS, Park M, Song J-H. Modulation of sodium currents in rat sensory neurons by nucleotides. Brain Research. 2004;1006(2):168–76.

[102] Beamer E, Gölöncsér F, Horváth G, Bekő K, Otrokocsi L, Koványi B, Sperlágh B. Purinergic mechanisms in neuroinflammation: an update from molecules to behavior. Neuropharmacology. 2016;104:94–104.

[103] Jacobson, KA, and Müller CE. Medicinal chemistry of adenosine, P2Y and P2X receptors. Neuropharmacology. 2016;104:31–49.

[104] Boccazzi M, Rolando C, Abbracchio MP, Buffo A, Ceruti S. Purines regulate adult brain subventricular zone cell functions: contribution of reactive astrocytes. Glia. 2014;62(3):428–39.

[105] Burnstock G. An introduction to the roles of purinergic signalling in neurodegeneration, neuroprotection and neuroregeneration. Neuropharmacology. 2016;104:4–17.

[106] Fumagalli M, Lecca D, Abbracchio MP. CNS remyelination as a novel reparative approach to neurodegenerative diseases: the roles of purinergic signaling and the P2Y-like receptor GPR17. Neuropharmacology. 2016;104:82–93.

[107] Vrbova G, Mehra N, Shanmuganathan H, Tyreman N, Schachner M, Gordon T. Chemical communication between regenerating motor axons and Schwann cells in the growth pathway. European Journal of Neuroscience. 2009;30(3):366–75.

[108] Abbracchio MP, Burnstock G, Verkhratsky A, Zimmermann H. Purinergic signalling in the nervous system: an overview. Trends in Neurosciences. 2009;32(1):19–29.

[109] Förster D, Reiser G. Supportive or detrimental roles of P2Y receptors in brain pathology? – The two faces of P2Y receptors in stroke and neurodegeneration detected in neural cell and in animal model studies. Purinergic Signalling. 2015;11(4):441–54.

[110] Giaume C, Kirchhoff F, Matute C, Reichenbach A, Verkhratsky A. Glia: the fulcrum of brain diseases. Cell Death & Differentiation. 2007;14(7):1324–35.

[111] Guzman SJ, Gerevich Z. P2Y receptors in synaptic transmission and plasticity: therapeutic potential in cognitive dysfunction. Neural Plasticity. 2016;2016.

[112] Weisman GA, Camden JM, Peterson TS, Ajit D, Woods LT, Erb L. P2 receptors for extracellular nucleotides in the central nervous system: role of P2X7 and P2Y2 receptor interactions in neuroinflammation. Molecular Neurobiology. 2012;46(1):96–113.

[113] Weisman GA, Woods LT, Erb L, & Seye CI. P2Y receptors in the mammalian nervous system: pharmacology, ligands and therapeutic potential. CNS & Neurological Disorders-Drug Targets (Formerly Current Drug Targets-CNS & Neurological Disorders). 2012b;11(6):722–38.

[114] Kobayashi K, Yamanaka H, Yanamoto F, Okubo M, & Noguchi, K. Multiple P2Y subtypes in spinal microglia are involved in neuropathic pain after peripheral nerve injury. Glia. 2012;60(10):1529–39.

[115] Moriyama T, Iida T, Kobayashi K, Higashi T, Fukuoka T, Tsumura H, et al. Possible involvement of P2Y2 metabotropic receptors in ATP-induced transient receptor potential vanilloid receptor 1-mediated thermal hypersensitivity. Journal of Neuroscience. 2003;23(14):6058–62.

[116] Lecona E, Turnay J, Nieves O, GuzmÃ¡n-ArÃ¡nguez A, Morgan RO, Fernandez M-P, et al. Structural and functional characterization of recombinant mouse annexin A11: influence of calcium binding. Biochemical Journal. 2003;373(2):437–49.

[117] Abbracchio MP, Boeynaems JM, Barnard EA, Boyer JL, Kennedy C, Miras-Portugal MT, … & Burnstock G. Characterization of the UDP-glucose receptor (re-named here the P2Y 14 receptor) adds diversity to the P2Y receptor family. Trends in Pharmacological Sciences. 2003;24(2):52–5.

[118] Chambers JK, Macdonald LE, Sarau HM, Ames RS, Freeman K, Foley JJ, … & Trill J. AG protein-coupled receptor for UDP-glucose. Journal of Biological Chemistry. 2000;275(15):10767–71.

[119] Sponne IE, Gaire D, Stabler SP, Droesch S, Barbé FM, Allen RH, … & Nicolas JP. Inhibition of vitamin B12 metabolism by OH-cobalamin c-lactam in rat oligodendrocytes in culture: a model for studying neuropathy due to vitamin B12 deficiency. Neuroscience Letters. 2000;288(3):191–4.

[120] Banerjee R, Ragsdale SW. The many faces of Vitamin B12: catalysis by cobalamin-dependent enzymes 1. Annual Review of Biochemistry. 2003;72(1):209–47.

[121] Clarke R, Smith AD, Jobst KA, Refsum H, Sutton L, Ueland PM. Folate, vitamin B12, and serum total homocysteine levels in confirmed Alzheimer disease. Archives of Neurology. 1998;55(11):1449–55.

[122] Justo R, Cesar M, Migowski E, Cisne R. Relation between vitamins of the b complex, GABA and glutamate, and their role in neurocognitive disorders-Brief review. International Journal of Basic and Applied Sciences. 2016;5(4):229–37.

[123] Ross J, Baldessarini MD. Neuropharmacology of S-adenosyl-L-methionine. The American Journal of Medicine. 1987;83(5):95–103.

[124] Surtees R. Biochemical pathogenesis of subacute combined degeneration of the spinal cord and brain. Journal of Inherited Metabolic Disease. 1993;16(4):762–70.

[125] Kumar N. Neurologic aspects of cobalamin (B12) deficiency. Handbook of Clinical Neurology. 2013;120:915–26.

[126] Fortun J, Verrier JD, Go JC, Madorsky I, Dunn WA, Notterpek L. The formation of peripheral myelin protein 22 aggregates is hindered by the enhancement of autophagy and expression of cytoplasmic chaperones. Neurobiology of Disease. 2007;25(2):252–65.

[127] Goldberg H, Júnior ABS, Cohen JC, Rzetelna H, Mezitis SGE, Nunes FP, Ozeri D, Daher JPL, Nunes CP, Oliveira L, Geller M. Neural compression-induced neuralgias: clinical evaluation of the effect of nucleotides associated with vitamin B12. Revista Brasileira de Medicina. 2009;66(11):380–5.

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