Volume : 5 | Issue : 7 | July 2016 • ISSN No 2277 - 8179 | IF : 3.508 | IC Value : 69.48

Cotransmitters in Ans: A Review of Therapeutic Potentials of Adenosine and Nitric Oxide

Pharmacology

KEYWORDS : Adenosine, autonomic nervous system, cotransmitters, nitric oxide, therapeutic potentials.

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ABSTRACT

The role of co-transmitters in health and disease is increasingly being appreciated. This review was aimed at highlighting the therapeutic potentials of adenosine and nitric oxide. Previous works and research findings on this subject assessed through Google Search, Pubmed, Hinari websites as well as standard textbooks on Pharmacology provided the needed information in the process of this review. The review unavoidably strayed into cotransmitters in CNS. Therapeutic uses of cotransmitters, their agonists or antagonists, in the treatment of diverse diseases were evaluated. Such therapeutic uses included adenosine receptor agonists for supraventricular arrhythmias, adenosine receptor antagonist for bronchial asthma, adenosine uptake inhibitors and adenosine kinase inhibitor for pain/allodynia, adenosine receptor antagonist for Parkinson's disease and GLP-1 analog for type 2 DM, as well as nitric oxide, and nitric oxide synthase inhibitors and scavengers for primary pulmonary hypertension and sepsis-induced septic shock respectively.

Introduction

It is now established that neurones on stimulation release more than one neurotransmitter – the primary neurotransmitter and the cotransmitter[1,2]. The latter are chemical mediators released in addition to the primary neurotransmitter after nervous stimulation. Chemical entities acting as cotransmitters include purines (ATP, ADP, Adenosine), peptides (substance P; Neuropeptide Y, NY; vasoactive intestinal peptide, VIP), Nitric oxide (NO), 5-hydroxytryptamine (5HT, Serotonin), among others[3]. Traditional neurotransmitters such as acetylcholine and norepinephrine may also act as co-transmitters. A neurotransmitter could act as primary neurotransmitter in one location and as co-transmitter in another. For example, in the vas deferens ATP serves as the primary transmitter that mediates fast synaptic transmission, while noradrenaline functions as modulatory co-transmitter[4].

Cotransmitters occur throughout the nervous system but have been studied more in the autonomic nervous system (ANS). For example, the roles of cotransmitters are established in the ENS, sympathetic ganglia, coronary and systemic vasculature, renal tubular transport.

The idea of co-transmitters was first muted in the mid-seventies when Geoff Burnstock identified ATP as a non-adrenergic non-cholinergic (NANC) transmitter[4]. Later on, it was observed that autonomic transmitter functions in many organs could not be completely blocked by drugs that abolish the response to the primary neurotransmitters[5]. More evidence for cotransmission includes the following: (a) The candidate neurotransmitters were detected within nerve fibres that innervate target tissues, e.g. ATP and noradrenaline were detected in sympathetic nerves supplying the vas deferens of the rabbit[6]. (b) Such neurotransmitters were recovered upon micro-dialysis or in the venous effluent following electrical stimulation of the organ.

The functional advantages of cotransmitters are increasingly being appreciated. In general, they provide faster or slower response to supplement or modulate the effect of primary neurotransmitters. For instance, one of the neurotransmitters may be degraded faster than the other. Cotransmission, therefore, allows a single nerve stimulation to produce longer lasting effect.

Also, the release of neurotransmitters varies according to frequency of stimulation: co-transmitters are preferentially released at higher frequency of stimulation than primary transmitters. For example, stimulation of the sympathetic nerve of guinea pig vas deferens produces a biphasic contractile response which is mediated by two neurotransmitters: fast initial twitch mediated by ATP and a slow tonic phase mediated by noradrenaline[7]. This biphasic response produced by cotransmitters allows for smoother control of physiological functions.

It was traditionally thought that cotransmitters were co-stored and co-released from the same synaptic vesicle. Experimental evidence, however, suggest that this is not so. This explains the biphasic contractile response quoted above[8]. For example, an α_2-adrenoceptor agonist, xylazine, produced a greater reduction of ATP release than of noradrenaline, suggesting that both are deferentially released[9,6]. The co-transmitters under review were restricted to adenosine and nitric oxide for want of space and time. The review unavoidably strayed into the roles of these neurotransmitters in the central nervous system (CNS).

Adenosine and nitric oxide in normal physiology

In 1929, Drury and Szeut-Gyorgi reported that adenosine reduced cardiac contractility, increased coronary vasodilatation, inhibited intestinal smooth muscle contraction as well as elicited CNS sedation in pigs[10]. Adenosine Inhibits production of pro-inflammatory cytokines (IL-1, IL-6, IL-12) by immune cells[11], and suppresses the release of inflammatory mediators by inhibiting lymphoid or myeloid cells including neutrophils, macrophages, lymphocytes and platelets. Other physiological functions of adenosine include modulation of cytokine production[12], inhibition of cardiac AV conduction and reduction of force of contraction, stimulation of gut and cardiac nociceptive afferent neorones[13]. Adenosine release in response to ischaemia has been suggested as a mechanism of angina pectoris[14]. It produces bronchoconstriction and the bronchodilator effect of methylxanthines is attributed to the inhibition of adenosine receptors[15].

In the nervous system adenosine inhibits transmitter release in nervous synapses: it is a potent inhibitor of dopamine, glutamate, acetylcholine, serotonin and noradrenaline. In the CNS, this translates to reduced motor activity, depressed respiration, hypnosis and anxiolysis. By inhibiting glutamate release in the CNS, adenosine protects the neurones by promoting ischaemic preconditioning[16]. Hypnotic and sedative effects of adenosine are supported by findings that sleep deprivation increases A_1 receptor density in the cortex and corpus striatum and extracellular aden-

osine concentration increases in basal forebrain in proportion to periods of sustained wakefulness[17,18].

Nitric oxide (NO) is formed by nitric oxide synthase (NOS) from L-arginine and molecular oxygen. It exists in one inducible form (iNOS) and two constitutive forms (eNOS and nNOS). The inducible NOS, produced in response to trauma and infections, is usually found in immune cells and smooth muscles. On the other hand, the constitutive forms, produced in response to shear stress, are predominant in endothelial cells, cardiac myocytes, and osteoblasts.

Nitric oxide reacts rapidly with superoxide anion (0_2^-) to produce peroxynitrite anion ($ONOO^-$) which is responsible for many of its toxic effects.

Nitric oxide causes vasodilation by activating guanyl cyclase which results in increased cGMP and consequent vascular smooth muscle relaxation. Consequently, nitric oxide released by pelvic nerves mediates penile erection. It also causes bronchodilation which at high doses causes pulmonary edema[19]. Among other factors, nitric oxide-mediated dilatation of cranial blood vessels contributes to pathogenesis of migraine. It inhibits platelet aggregation and expression of adhesion molecules thereby reducing endothelial monocyte adhesion, thrombosis, and formation of athermanous plagues. These actions inhibit the inflammatory processes. Consequently, nitric oxide levels are increased in asthma, inflammatory bowel disease and chronic arthritis in an attempt to arrest the ongoing inflammatory processes that characterize these conditions[20,21].

On the other hand, nitric oxide increases cell growth. This has been substantiated by findings that nitric oxide donors such as isosorbide dinitrate IISDN) and guaifenesin dinitrate (GDN) increase muscle cell activation and proliferation[22]. Endogenous nitric oxide promotes tumor progression and metastasis through stimulation of tumor cell migration and angiogenesis *in vitro*[23].

In the immune system, nitric oxide is involved in nonspecific host defences by nitrosylation of nucleic acids and haem-containing enzymes of invading micro-organisms[24].

In the CNS, N-methyl-D-aspartate, (NMDA) receptor-mediated activation of nNOS is involved in long term potentiation (LTP) and synaptic plasticity which are important in memory and learning respectively[25,26].

Adenosine and nitric oxide in disease

Adenosine exerts anti-inflammatory actions in many tissues, especially the bronchial and gastrointestinal smooth muscles. In fact, the anti-inflammatory effects of drugs such as methotrexate and sulfasalazine are, in part, mediated via the release of adenosine[27].

Adenosine induces bronchoconstriction in asthmatics, but not in normal airways. This is supported by the fact that adenosine levels are increased in broncho-alvedar lavage fluid of patients with allergic asthma. In addition, all four adenosine receptors are expressed in the lungs of patients with pulmonary hypertension, especially primary pulmonary hypertension of the newborn, PPHN[28]. Also, theophylline (non-selective adenosine antagonist) improves lung function in human asthmatics by inhibiting the bronchoconstrictor effect of endogenous adenosine.

There is evidence linking defective adenosine production with inflammatory bowel disease[29,30]. In some studies, the inhibition of adenosine degradation by inhibition of adenosine deaminase (ADA) was able to protect colonic tissues from inflammatory injury in experimental colitis induced by dinitrobenzene sulphonic acid[31,28]. To support this view, Alam et al. demonstrated that adenosine ameliorated inflammatory bowel disease (IBD) by reducing colonic levels of pro-inflammatory cytokines IL-1, IL-6, and IL-12[32].

Adenosine is an inhibitory modulator of brain activity and is therefore considered an endogenous anticonvulsant of the brain with neuroprotective functions[33]. This neuroprotective effect of adenosine is mediated by stabilization of neuronal membrane and inhibition of excitatory amino acid release, hyperpolarization of astrocyte cell membranes, modulation of cerebral blood flow, inhibition of platelet aggregation, as well as increase in the synthesis and release of neurotrophic nerve growth factor[34]. On the other hand, adenosine antagonists such as theophylline are CNS stimulants and enhance cognition, but can easily lead to excitotoxicity and neuronal death[35].

Astroglyosis (an abnormal increase in the number of astrocytes due to the destruction of nearby neurons in the CNS) is associated with up-regulation of adenosine kinase which leads to reduction in adenosine levels[36]. This is often the scenario in epilepsy secondary to CNS trauma, infection, ischemia, stroke, autoimmune responses, and neurodegenerative diseases[37]. Adenosine attenuates ischaemia and reperfusion injury by improving tissue perfusion via vasodilation (ischaemic preconditioning) and by its anti-inflammatory action[38,39]. Therefore, adenosine deficiency predisposes to ischaemic injury and neuronal death.

Adenosine inhibits nociception[40]. For instance, glutamate and substance P, key mediators of pain sensation and abnormal hyper-excitability, are reduced by adenosine and its agonists[41]. Also, allodynia (pain due to a stimulus which does not normally produce pain) is associated with reduced tissue adenosine levels and can be ameliorated by treatment with adenosine kinase inhibitors such as 5-iodotubercidin[42].

Increased or reduced nitric oxide also contributes to disease conditions. For instance, excessive nitric oxide production often leads to hypotension and shock[43]. It also causes release of excessive glutamate which results in neuronal excitotoxicity due to excessive stimulation of NMDA receptors. This occurs in some neurodegenerative disorders such as Alzheimer disease[44]. Nitric oxide is also involved in the regulation of neuronal development. Therefore, underproduction of NO has been reported in patients with hypertrophic pyloric stenosis and achalasia which are conditions resulting from failure of migration of nitric oxide-sensitive inhibitory ganglion cells to the oesophageal sphincter[45,46]. Nitric oxide dysfunction is also incriminated in the pathogenesis of eclampsia as well as erectile dysfunction in diabetic patients[47].

In arthritis, there is accumulated evidence that NO is produced locally within the joints by chondrocytes and infiltrating leucocytes[48]. Peroxynitrites released into the joint space from metabolism of nitric oxide during inflammation of the joints have been linked to destruction of chondrocytes and endothelial surfaces. The cellular destructive properties of peroxynitrites on pancreatic islet B-cells are also implicated in type 2 diabetes mellitus[20,49].

Therapeutic uses of adenosine and nitric oxide

The role of adenosine and nitric oxide in various disease processes has been established. While some disease processes are caused by neurotransmitter hyperfunction, oth-

Volume : 5 | Issue : 7 | July 2016 • ISSN No 2277 - 8179 | IF : 3.508 | IC Value : 69.48

ers are caused by their hypofunction. Therefore, the neurotransmitters as well as their agonists and antagonists are being increasingly used in the therapeutic management of such disorders.

The following are some diseases in which the neurotransmitters, their agonists or antagonists have been found useful. Many are still investigational.

Adenosine is drug of choice for termination of supraventricular tachycardia. It is safer than alternative drugs such as β-adrenoceptor antagonists or verapamil because of its short duration of action[50]. Consequently, ***1B-MECA*** (A_3 receptor agonist) is useful in treatment of cardiac ischaemia[51,52].

Theophylline and ***bamiphylline*** (both adenosine receptor antagonists) produce bronchodilation and improve lung function at therapeutic levels less than that required to inhibit phosphodiesterase[28].

As stated above, adenosine and nitric oxide contribute to the control of gastrointestinal motility, secretions, blood flow, sensation, and immune function[13]. Expectedly, Hasko et al. demonstrated that IB-MECA (A_3 receptor agonist) produced significant amelioration of experimentally induced inflammation in mice[53]. On the perception of pain, adenosine inhibits nociceptive processes in the brain and spinal cord**.** An experimental adenosine agonist ***(R-PIA)*** reduces allodynia in neuropathic patients. It has also been demonstrated that low dose infusions of perioperative adenosine reduced the requirement for volatile anesthesia and for postoperative opioid analgesia[54]. In addition, adenosine kinase inhibitors (***NH2dADO*** and **5-IT)** reduced tactile allodynia in a rat model of diabetic neuropathic pain[55].

The role of adenosine in the pathogenesis of epilepsy is worthy of mention. Whereas ATP is an excitatory neurotransmitter which participates in pathological neuronal hyper-excitability associated with seizures, adenosine is inhibitory and is considered an endogenous anticonvulsant. Therefore, substances that increase intracellular concentrations of adenosine are considered putative anticonvulsant agents. For example, adenosine kinase inhibitor, ***NH-2dADO,*** reduced bicuculline methionide-induced seizures in mice[56,57,58]. Expectations are high that adenosine kinase inhibitors will soon become useful in the clinical management of the epilepsies.

Co-localization of adenosine A_{2A} and dopaminergic D_2 receptors in the striatum creates antagonistic interaction between adenosine and dopamine. Therefore, simultaneous activation of dopaminergic D_2 receptors and inhibition of adenosine A_{2A} receptors is expected to ameliorate the symptoms of Parkinsonism. ***Istradefylline*** (KW – 6002), A_2 receptor antagonist, is now approved as mono- or combination therapy for Parkinson's disease[59,60]. Recently, clinical trials with positive outcome were completed on the use of istradefylline (KW-6002) as an anti-Parkinson drug[61].

Experimental studies showed that there is increase in circulating adenosine levels during migraine headache[62]. Therefore, the use of adenosine antagonists, alone or as adjuncts ameliorates migraine[63].

Nitric oxide released during sepsis acts as anti-microbial agent. Unfortunately, it also acts as a vasodilator and an anti-inflammatory agent thus contributing to septic shock. For that reason, the endogenous nitric oxide synthase inhibitors *N-monomethyl-L-arginine* (L-NMMA) and ADMA were suggested to be used in experimental sepsis to raise blood pressure and restore vasomotor tone[64,65]. For instance, in a randomized, double-blind, placebo-controlled multicenter study**,** Bakker et al. demonstrated that nitric oxide synthase inhibitor NG-methyl-L-arginine hydrochloride (546C88) promoted the resolution of shock in patients with severe sepsis[66]. However, other studies reported negative results. In fact, both the endogenous and synthetic nitric oxide inhibitors (L-NMMA and ADMA, L-NAME and L-NArg respectively) gave disappointing results in clinical trials of septic shock[67,68,69].

Other methods of inhibiting nitric oxide action include the inhibition of guanyl cyclase and the use of nitric oxide scavengers. Methylene blue and the grape see extract (proanthocyanidins) inhibit the activation of soluble guanyl cyclase thereby inhibiting the conversion of GMP to cGMP thereby preventing the cGMP-mediated vascular smooth muscle relaxation[70,71].

Nitric oxide and adenosine cause pulmonary vasodilation by increasing cGMP and cAMP respectively. In addition, both stimulate K^+ATP channels in vascular smooth muscles, resulting in hyperpolarization and smooth muscle relaxation. In PPHN pulmonary vascular resistance remains high during neonatal period. Adenosine infusion or nitric oxide inhalation ameliorates this condition by increasing intracellular cAMP which produces pulmonary vascular vasodilation[72]. Also, ***adenosine*** contributes to mucociliary clearance in the airways[73].

Conclusion

It is now established that co-transmitters play important roles in pathophysiology of many chronic illnesses such as inflammatory bowel disease, arthritis, asthma, epilepsy, Parkinson's and Alzheimer's disease. At present, most of these diseases are not amendable to permanent cure.

Therefore their prevention through application of these neurotransmitters, their agonists or antagonists will go a long way in reducing the burden of these chronic diseases on the society. For instance, nucleotidase inhibitors need to be developed. Such inhibitors will prolong the action of ATP and adenosine just in the same manner that anticholinesterases potentiate the effect of endogenous acetylcholine.

NOS isoform-selective inhibitors should be developed as non-selective inhibitors have both desirable and undesirable effects. For example, inhibition of iNOS is desirable in sepsis and inflammation while inhibition of eNOS results in vasoconstriction and ischaemic damage. Specific inhibitors of iNOS, when prepared as cream for local application will ameliorate cases of chronic arthritis, thereby avoiding serious adverse effects associated with NSAIDs.

The A_2 receptor antagonist, istradefylline, when combined with D_2 receptor agonist in treatment of Parkinson's disease offers obvious advantage as it avoids the unwanted anticholinergic adverse effects often associated with anticholinergics.

Finally, many of these cotransmitters acting as novel therapeutic agents are still undergoing clinical trials. It is hoped that such trials become successful very soon.

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Volume : 5 | Issue : 7 | July 2016 • ISSN No 2277 - 8179 | IF : 3.508 | IC Value : 69.48

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