Effect of adenosine receptors modulation on neurological actions of theophylline in rats

Alanazi Waleed Ahmed K

Northern Borders University, Saudi Arabia, E-mail: Al-lodah12@hotmail.com

Abstract

Aim of the study: Theophylline, a methyl xanthine derivative which was widely utilized in the treatment of asthma and bronchopulmonary obstructive diseases, is understood to supply seizures which could result to non-selective antagonistic effect on central adenosine receptors. This study provides an insight on the importance of how modulation of adenosine receptors might affect the neurological actions of theophylline and consequently might clarify a possible mechanistic approach to theophylline. Methods: This was applied by studying the effect of pretreatment of rats with adenosine and its analogs on theophylline-induced seizures. Acute toxicity of theophylline in rats was studied by determination of median convulsive dose (CD50) of theophylline alone and after pretreatment of rats with adenosine and its analogs. The marginal dose of theophylline that elicits convulsions (i.e., the smallest amount convulsive dose) and therefore the serum level of theophylline at this dose were determined. Results: Pretreatment of rats with adenosine, 2-CADO, CPA and CPCA failed to significantly offer protection against convulsions induced by acute challenge with theophylline in a very dose of 200 mg/kg.

Conclusion: Significant elevation of CD50 of theophylline after pretreatment of rats with adenosine and CPA isn't conforming with the observation that adenosine and its analogs didn't significantly offer protection against theophylline-induced seizures and this means that further investigations are needed to review role of adenosinergic system in theophylline-induced seizures. Theophylline is given systemically (orally as slow-release preparations for chronic treatment and intravenously for acute exacerbations of asthma) and blood concentrations are determined mainly by hepatic metabolism, which can be increased or decreased in several diseases and by concomitant drug therapy. Theophylline is now usually used as an add-on therapy in asthma patients not well controlled on inhaled corticosteroids and in COPD patients with severe disease not controlled by bronchodilator therapy. Side effects are associated with plasma concentrations and include nausea, vomiting and headaches because of PDE inhibition and at higher concentrations to cardiac arrhythmias and seizures thanks to adenosine A1-receptor antagonism. Theophylline (3-methyxanthine) has been wont to treat airway diseases for over 70 years. it had been originally used as a bronchodilator but the relatively high doses required are related to frequent side effects, so its use declined as inhaled β2-agonists became more widely used.

Therefore, the combined effects of endogenously produced adenosine could end in a decrease of both substrate mobilization and utilization, resulting in reductions in both shivering and nonshivering thermogenesis and reduced cold tolerance. Conversely, the employment of an adenosine antagonist, like THEO, could lead to improved cold tolerance. In support of this scheme, we've shown that 1) pretreatment with a particular adenosine receptor antagonist (8-phenyltheophylline), but not a phosphodiesterase inhibitor (enprofylline), significantly enhanced thermogensis and improved cold resistance kind of like the advance after THEO pretreatment Adenosine is implicated within the modulation of cardiovascular responses either at the peripheral or at central level in experimental animals. However, there

aren't any dedicated reviews on the involvement of adenosine in mediating the hypotensive response of centrally administered clonidine normally and specifically in aortically barodenervated rats (ABD). The conscious ABD rat model exhibits surgically induced baroreflex dysfunction and exaggerated hypotensive response, compared with conscious sham-operated (SO) rats. the present review focuses on, the role of adenosine receptors in pressure level (BP) regulation and their possible crosstalk with other receptors e.g. imidazoline (I1) and alpha (α2A) adrenergic receptor (AR). the previous receptor may be a molecular target for clonidine, whose hypotensive effect is enhanced approx. 3-fold in conscious ABD rats. We also discussed how the balance between the brain stem adenosine A1 and A2A receptors is regulated by baroreceptors and the way such balance influences the centrally mediated hypotensive responses. the employment of the ABD rat model yielded insight into the downstream signaling cascades following clonidine-evoked hypotension during a surgical model of baroreflex dysfunction. The effect within the trigeminal nucleus reflects a central action, whilst inhibition of CGRP release is probably going to be because of an action at adenosine A1 receptors on peripheral terminals of the trigeminal. Both effects are keep with the concept of adenosine A1 receptors being located prejunctionally on primary afferent neurons and causing inhibition of transmitter release. Adenosine A1 receptor agonists, like GR-79236, haven't any effect on resting arterial blood vessel diameter in rats.85 Moreover, GR-79236 can inhibit the nociceptive trigeminal blink reflex at doses in humans52 that are both trigeminally inhibitory and without vascular effects in experimental animals. Theophylline or DPCPX reversed the results of both R-PIA and dipyridamole on rate of respiration, regularity of rate of respiration, inspiratory time, amplitude, and intra-burst frequency of I neurons. Thus, adenosine depresses both the I neurons within the rostral ventrolateral medulla and therefore the respiratory motor output. This depression of I neurons and rate of respiration are often abolished by theophylline primarily through a blockade of medullary adenosine A1 receptors. An age-dependent correlation of the consequences of R-PIA and dipyridamole, with a more pronounced decrease in respiratory activity in preparations from younger animals, indicates that adenosinergic modulation of medullary respiration-related neurons changes during the primary days of postnatal life.