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Minireview

Using caffeine and other adenosine receptor antagonists and agonists as therapeutic tools against neurodegenerative diseases: A review

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ABSTRACT

Caffeine is the most consumed pychostimulant in the world, and it is known to affect basic and fundamental human processes such as sleep, arousal, cognition and learning and memory. It works as a nonselective blocker of adenosine receptors (A1, A2a, A2b and A3) and has been related to the regulation of heart rate, the contraction/relaxation of cardiac and smooth muscles, and the neural signaling in the central nervous system (CNS). Since the late 1990s, studies using adenosine receptor antagonists, such as Caffeine, to block the A1 and A2a adenosine receptor subtypes have shown to reduce the physical, cellular and molecular damages caused by a spinal cord injury (SCI) or a stroke (cerebral infarction) and by other neurodegenerative diseases such as Parkinson's and Alzheimer's diseases. Interestingly, other studies using adenosine receptor agonists have also shown to provide a neuroprotective effect on various models of neurodegenerative diseases through the reduction of excitatory neurotransmitter release, apoptosis and inflammatory responses, among others. The seemingly paradoxical use of both adenosine receptor agonists and antagonists as neuroprotective agents has been attributed to differences in dosage levels, drug delivery method, extracellular concentration of excitatory neurotransmitters and stage of disease progression. We discuss and compare recent findings using both antagonists and agonists of adenosine receptors in animal models and patients that have suffered spinal cord injuries, brain strokes, and Parkinson's and Alzheimer's diseases. Additionally, we propose alternative interpretations on the seemingly paradoxical use of these drugs as potential pharmacological tools to treat these various types of neurodegenerative diseases.

Contents

Spinal cord injury (SCI)

Spinal cord injury (SCI) is the main cause of disability worldwide producing mainly mechanical and physical damage, which may lead to inflammation and neuronal cell death (Palacios et al., 2012). Adenosine receptors have been shown to have a major role in regulating the inflammatory responses after a SCI (Song et al., 2009). For example,

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the blockade of the A1 adenosine receptor by caffeine has been involved in mediating neuroprotective effects against SCI, including reduction of hyperalgesia, which involves an attenuation of hypersensitivity to pain, usually caused by damage to nociceptors (pain receptors) and/or peripheral nerves after injury (Palacios et al., 2012; Stone et al., 2009). Also, daily caffeine intake in mice has been shown to inhibit the process of antinociception (increased tolerance to pain) by modulation of the A1 receptor as demonstrated using the specific A1 receptor antagonist DPCPX, which mimicked the effects of caffeine (Salvemini et al., 2013). In addition, caffeine application to the spinal cord of guinea pigs after a SCI induced an up-regulation of the A1 receptor and of tissue growth factor (TGF)-beta mRNAs, which has been shown to provide immune regulation of inflammation further supporting a neuroprotective role of caffeine (Butler and Prendergast, 2012; Chen et al., 2010; Salvemini et al., 2013). These findings suggest a role of the A1 adenosine receptor as a key target for the regulation of pain and the inflammatory response that ensues in patients after suffering a SCI (Fig. 1).

Regulation of the adenosine A2a receptor has been implicated in the modulation of the anti-inflammatory or proinflammatory responses having a protective role against tissue damage and locomotor dysfunction in animal models of SCI (Dai et al., 2010b; Pan and Chen, 2004). Pharmacological blockade of A2a receptors helps protect the CNS after a SCI by reducing excessive release of neurotransmitters caused by high levels of intracellular calcium ions, which can lead to neuronal death through increased excitability (excitotoxicity) (Pan and Chen, 2004). For example, enhanced release of the endogenous neurotransmitter adenosine soon after a SCI has been related to the development of many known functional motor and sensory deficits (Pan and Chen, 2004). Thus, the blockade of both A1 and A2a adenosine receptors has shown to provide a protective role against SCI-induced pain, inflammation and cell death caused by excessive neuronal activity.

The role of adenosine receptor agonists as potential neuroprotective agents against SCI has also been reported. A recent study showed that the intrathecal application of R(−)N6-(2-phenylisopropyl) adenosine (R-PIA), a selective A1 receptor agonist, inhibited SCI-induced hyperalgesia in rats (Higashi et al., 2002). On the contrary, the intrathecal application of CGS21680, a selective A2a receptor agonist, did not inhibit SCI-induced hyperalgesia, suggesting that adenosine inhibits hyperalgesia through the specific activation of A1 receptors (Higashi et al., 2002). Although there is a substantial body of work showing the

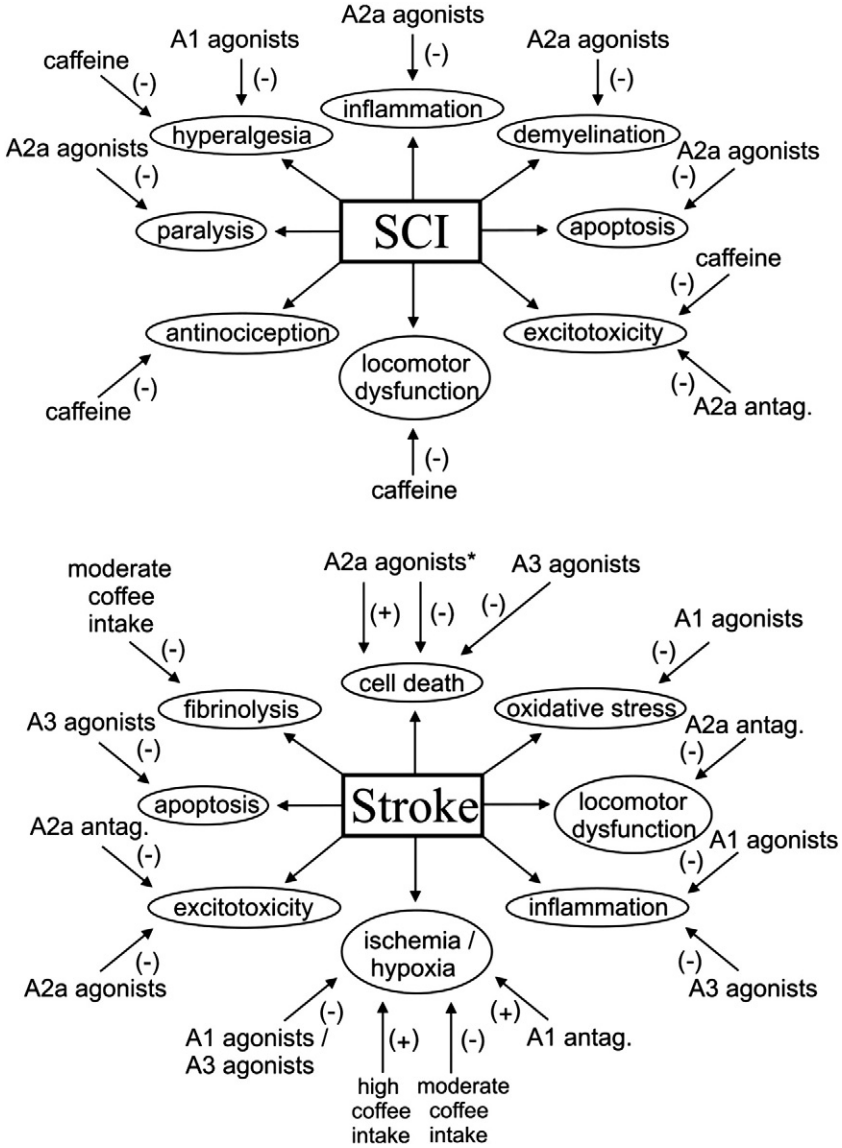

Fig. 1. Summary of the reported results of using adenosine receptor agonists and antagonists to treat the main detrimental effects caused by a spinal cord injury, stroke, and Parkinson's and Alzheimer's diseases. *The effects of A2a receptor agonists on cell death caused by a stroke have been shown to include a neuroprotective role in acute experiments and a neurally detrimental role in chronic experiments after brain damage (Stone et al., 2009).