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Caffeine, A Drug for All Seasons

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Keywords

adenosine; adenosine receptors; caffeine; methylxanthines

Caffeine is the most widely used drug in the world and the most common caffeine delivery vehicle is coffee. Additional vehicles for caffeine delivery include carbonated soft drinks and "energy drinks." Interestingly, high doses of caffeine are banned from competitive sports as a performance enhancing drug, caffeine is included in a number of over-the-counter pain relievers and there are at least four psychiatric diagnoses associated with caffeine use. Thus, it comes as quite a surprise to most people that drinking coffee is associated with diminished mortality and that protection from death due to liver disease is the best documented contributor to reduced mortality. Although caffeine is the most extensively characterized pharmacologic agent in coffee, there are other active agents as well, and it has been difficult to capitalize on the hepatoprotective qualities of coffee without knowing which ingredient mediates the protective effect.

The recent demonstration by Modi and colleagues [1] that caffeine appears to protect from severe liver fibrosis in a case control study of patients seen at the NIH for treatment of chronic liver disease, primarily hepatitis C, offers at least a partial explanation for the protective effects of coffee. In their study Modi and co-workers observed that patients who consumed more than the 75th percentile of caffeine for the cohort (about 300 mg/day which is equivalent to the caffeine found in 2.25 cups of coffee) were significantly less likely to have severe hepatic fibrosis as defined by Ishak stage ≥3 (OR 0.33). Evidence for a protective effect of caffeine persisted even after correction for age, sex, race, type of liver disease, body mass index and alcohol ingestion (OR 0.25) and the protective effect was no less marked in the patients with HCV infection (OR 0.19). Although prior work had suggested that other agents (kahwol and cafestol) found in coffee might afford protection from hepatic fibrosis by altering the expression of hepatic enzymes involved in activation of agents (e.g. CCl_4) that cause fibrosis in animals [2], the authors were unaware of prior work indicating the direct effects of caffeine on hepatic fibrosis *in vivo*. In this series, coffee was the greatest single source of caffeine and

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Disclosures: Dr. Cronstein holds or has filed applications for patents on the use of adenosine A_{2A} receptor agonists to promote wound healing and use of A_{2A} receptor antagonists to inhibit fibrosis; use of adenosine A_1 receptor antagonists to treat osteoporosis and other diseases of bone; the use of adenosine A_1 and A_{2B} Receptor antagonists to treat fatty liver, and; the use of adenosine A_{2A} receptor agonists to prevent prosthesis loosening. **Consultant (within the past two years)** King Pharmaceutical (licensee of patents on wound healing and fibrosis above). CanFite Biopharmaceuticals, Savient Pharmaceuticals, Bristol-Myers Squibb, Roche Pharmaceuticals, Cellzome, Tap (Takeda) Pharmaceuticals, Prometheus Laboratories, Regeneron (Westat, DSMB), Sepracor, Amgen, Endocyte, Protalex, Allos, Inc., Combinatorx, Kyowa Hakka.,. **Honoraria/Speakers' Bureaus:** Tap (Takeda) Pharmaceuticals. **Stock**: CanFite Biopharmaceuticals received for membership in Scientific Advisory Board.

other sources contributed far less caffeine. Because coffee was the dominant source of caffeine in this group of patients, there was only a trend towards an impact for the contribution of other sources of caffeine toward the protection from fibrosis.

The pharmacologic properties of caffeine have been explored for many years and a variety of different pharmacologic mechanisms have been ascribed to caffeine. The most well known and better understood pharmacologic effect of caffeine is the antagonism of adenosine receptors. Adenosine receptors were first described by Sattin and Rall [3], and it has subsequently become clear that there are four different types of adenosine receptors (A_1, A_{2A}, A_{2B} and A_3), all of which are members of the G protein coupled family of receptors [4]. Adenosine receptors are ubiquitous in their expression and they regulate a large number of physiologic functions.

Adenosine is a short-lived but abundant purine nucleoside that is released as a result of adenine nucleotide catabolism. Although hypoxia is the most well known stimulus for increasing extracellular adenosine levels, it has long been acknowledged that other types of cellular injury also induce adenosine release as adenine nucleotides are turned over and released. In the liver, adenosine is released as a result of the exposure to toxins, including ethanol and the hepatic fibrosing agents CCl_4 and thioacetamide [5]. Recent work from our laboratory has demonstrated that adenosine and its receptors (A_1 and A_{2B} receptors) play a central role in the development of hepatic steatosis in mice that chronically ingest high doses of ethanol [6]. In prior work, we and others have used a combination of specific adenosine receptor antagonists and adenosine receptor knockout mice to demonstrate a critical role for adenosine A_{2A} receptors in murine models of hepatic fibrogenesis [5,7]. Indeed, caffeine itself prevented hepatic fibrosis in response to CCl_4 and thioacetamide by, presumably, blocking adenosine receptor-mediated fibrosis [7]. Adenosine A_{2A} receptors are expressed in hepatic stellate cells and hepatocytes where they directly stimulate collagen production and induce [8–10]. Interestingly, all four adenosine receptors are expressed in human liver and the expression of adenosine A_{2A} and A_{2B} receptors is markedly increased in cirrhotic and steatotic livers [6].

Thus, the demonstration by Modi and colleagues [1] that caffeine ingestion prevents advanced liver fibrosis provides further supportive evidence for a role for adenosine receptors in hepatic fibrosis. Moreover, these findings suggest that more selective adenosine receptor agonists with more favorable pharmacokinetics might offer even greater protection from the development of hepatic fibrosis and cirrhosis.

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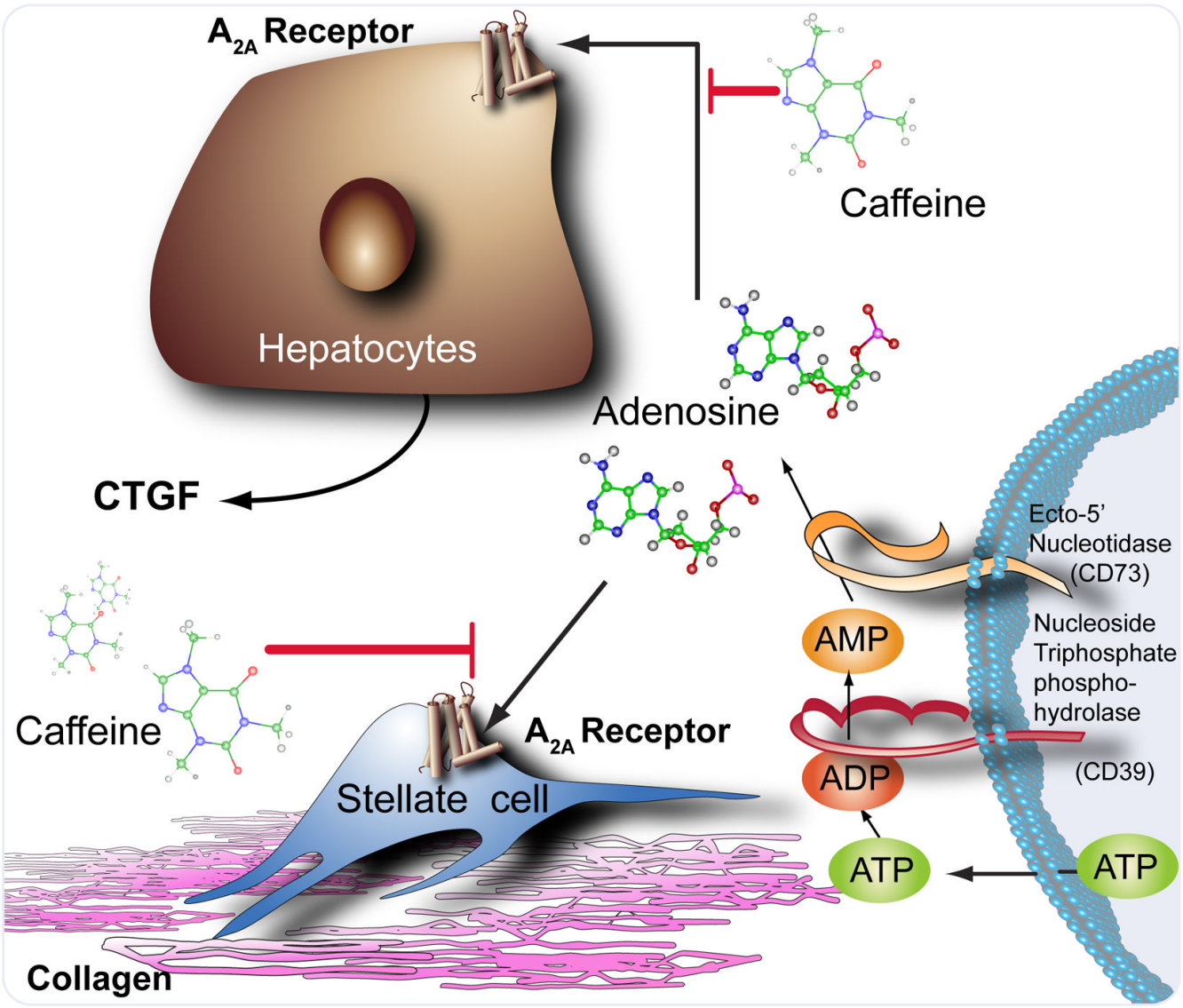

Figure 1.