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HOW DOES COFFEE PREVENT LIVER FIBROSIS? BIOLOGICAL PLAUSIBILITY FOR RECENT EPIDEMIOLOGICAL OBSERVATIONS

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The published epidemiological data demonstrating an inverse relationship between coffee (and potentially other caffeinated beverage) consumption and liver fibrosis and its downstream complications are weighty and rapidly accumulating. Several excellent recent reviews examine this evidence in great detail (1–3), and the overwhelming conclusion is that this inverse relationship is real – coffee drinking reduces liver fibrosis. Among the strongest studies to support this observation are the findings that, after adjustment for confounders, individuals in the highest quintile of caffeine consumption had less than one third the risk of ALT elevation of those in the lowest quintile (odds ratio (OR) 0.31, 95% CI 0.16–0.61) (4) and, perhaps more importantly, advanced liver fibrosis from chronic liver diseases of various etiologies is associated with reduced coffee and total caffeine consumption (5) with one study showing that the odds of having cirrhosis decreased with increasing daily consumption of coffee in a step-wise manner from an OR of 0.47 (95% CI 0.20–1.10) for patients consuming 1 cup of coffee per day to an OR of 0.16 (95% CI 0.05–0.50) for patients consuming 4 cups per day, compared to lifetime abstainers as the reference (OR 1.0) (6). Demonstrating the clinical significance of coffee consumption, Freedman and colleagues found that among patients with advanced fibrosis, those who consumed no coffee had a risk of hepatic decompensation or hepatocellular carcinoma (HCC) of 11.1 per 100 patient-years compared to just 6.3 per 100 patient-years in those consuming ≥ 3 cups of coffee per day, with no beneficial effect seen with tea or other sources of caffeine (7). Coffee consumption has also been shown to be associated with a lower risk of fatty liver disease (8), metabolic syndrome (9), and ultimately hepatocellular carcinoma (10). As a clinician or scientist interested in the pathogenesis of liver fibrosis, one may very well ask whether these findings are of great value.

Biological plausibility is the concept that an observed epidemiological association is “consistent with existing biological and medical knowledge” (11). This concept has long been considered a cornerstone in attempts to move epidemiological associations, even those that have been replicated on multiple occasions, to a high likelihood of causality (e.g., the now overwhelmingly accepted concept that tobacco smoking causes lung disease (12). Here we provide one of potentially several mechanisms by which coffee/caffeine consumption

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blocks liver fibrosis – that caffeine inhibits adenosinergic signaling in liver myofibroblasts – with strong hopes of providing biological plausibility for the observed epidemiological associations. We acknowledge fully that other potential mechanisms, such as antioxidant and anti-inflammatory properties of coffee constituents, are of possible importance; however, these concepts are not sufficiently developed at the level of observed science.

The beneficial effects of coffee and caffeine extract against liver fibrosis have been demonstrated by several studies using standard rodent models of experimental liver fibrosis induced by intoxication with dimethylnitrosamine (DMN), carbon tetrachloride (CCl_4), or thioacetamide (TAA) (13–18). In almost every study, ingestion of coffee blocked toxin-induced liver fibrosis/cirrhosis. Of note, conventional filtered coffee is the form generally used in most of the published studies supporting its protective role. In contrast to the above studies, one report showed that “Turkish style” unfiltered coffee consumption not only lacks any protective effect against CCl_4-induced liver fibrosis, but rather aggravates CCl_4-induced hepatotoxicity with significant AST and ALT elevation (19). Of note, the mechanism(s) underlying these differences was not studied, so more definitive animal experiments are highly warranted.

One mechanism by which coffee may protect against liver fibrosis is via alterations of liver signaling or inflammation. Transforming growth factor-β (TGF-β) is a major liver regulatory cytokine secreted in large quantities in standard rodent liver fibrosis models (20). TGF-β levels are reduced by coffee and caffeine administration to rats subjected to CCl_4-, DMN-, and TAA-induced liver fibrosis (13–18). One of the most significant downstream effects of TGF-β signaling is the activation of hepatic stellate cells (HSC) (21). In normal liver, HSC are vitamin A-rich, lipid-storing cells present in the space of Disse (22–24). In fibrosing liver, HSC undergo myofibroblastic differentiation and markedly upregulate secretion of extracellular matrix proteins, a process commonly known as HSC activation (24). When liver fibrosis models are performed on rodents exposed to coffee, total liver collagen contents are decreased (13–15, 18).

Activated HSC also secrete matrix metalloproteinases (MMPs), whose activity is essential to maintain the balance between tissue repair and scar formation in fibrotic livers (25). Total liver MMP secretion and activity are decreased by coffee consumption (13, 14). Expression of alpha-smooth muscle actin (α-SMA) protein is commonly used as a marker of HSC activation in the fibrotic liver (24). In the presence of coffee and caffeine, α-SMA total liver expression is diminished (13, 16, 18), potentially being indicative of reduced activation of HSCs and disease progression. Altogether, the *in vivo* studies reviewed here show that the anti-fibrotic properties of coffee/caffeine converge at a point in which HSC activation is diminished, providing biologic plausibility for the human studies cited above.

As noted above, coffee contains myriad chemical substances that could potentially be anti-fibrotic. A number of studies using experimental liver models have specifically addressed this question, by administration of decaffeinated coffee or caffeine solution to animals (13, 16, 19). Non-coffee caffeine was shown to protect liver against fibrosis in both TAA- and CCl_4-induced liver fibrosis in rats (16, 19, 26). On the other hand, several studies demonstrate that decaffeinated coffee is also protective, but to a lower extent than

caffeinated coffee in experimental animals (13, 19). Taken together, it appears that there are noteworthy holes in the animal liver fibrosis literature; there are simply not enough data to make firm conclusions about the relative importance of coffee caffeine content. At present, while it is premature to assume that the major effect of coffee is mediated by caffeine, the preponderance of evidence would suggest that this is the case.

Caffeine and other xanthines, including theophylline, have several known biological targets. These molecules have been characterized as non-selective antagonists of adenosine receptors (AR), inhibitors of phosphodiesterases, antagonists of the $GABA_A$ receptor, and stimulators of intracellular calcium release (27). While each of these effects is relevant to multiple biological processes, this section focuses on the antagonistic effects of caffeine on adenosine receptors, since this biological effect is relevant to the pathogenesis of liver fibrosis/cirrhosis.

Extracellular adenosine acts via four G-protein-coupled receptors (GPCRs), known as A_1, A_{2a}, A_{2b} and A_3 adenosine receptors to induce downstream effects (for recent review see (28, 29)). The A_1AR, A_{2a}AR and A_3AR are high-affinity receptors that respond to low concentrations (>10 nM) of extracellular adenosine, while A_{2b}AR is a low affinity receptor (>1 μM) thought to be selectively activated in pathological conditions (30). A_1AR and A_3AR are coupled to G proteins of the $G_{i/o}$ type, leading to downregulation of cAMP-dependent signaling pathways. In contrast, A_{2a}AR and A_{2b}AR increase the intracellular concentration of cAMP via G_s coupling. Interestingly, A_{2b}AR can also be coupled with G_q subunit to mobilize intracellular calcium (Ca^{2+}).

Experimental evidence of the antagonist effects of caffeine on adenosine receptors was first reported 40 years ago in the heart (31) and in the brain (32). Caffeine is a non-specific antagonist of all adenosine receptors. Specific synthetic agonists and antagonists derived from caffeine and other xanthine compounds have been developed for each AR and are now used as research tools in the studies of their functions, as well as potential therapeutic drugs (27). This is relevant, since specific antagonists of the A_{2a}AR inhibit experimental liver fibrosis (26, 33). In contrast, administration of A_1AR, A_{2b}AR and A_3AR specific antagonists does not significantly impact liver fibrosis progression (26). Thus, the anti-fibrotic effect of caffeine seems to be modulated by its antagonism of the A_{2a}AR. In addition, mice lacking A_{2a}AR expression are protected against liver fibrosis induced by CCl_4 and TAA (26). A potential role of the A_1AR in liver fibrosis is more controversial, as A_1AR deficient mice are also protected against CCl_4-induced liver fibrosis (34), but administration of the A_1AR specific antagonist DPCPX has no effect (26).

HSC are well established as primary effector cells during liver fibrosis. Interestingly, human HSC express mRNA for all four adenosine receptors ((35) and Dranoff JA unpublished data), among which A_{2a}AR is the most studied as a regulator of HSC function. Mouse HSC express all but A_3AR receptors (35). Thus, HSC represent a highly plausible cellular target mediating the anti-fibrotic effect of coffee/caffeine acting via adenosine receptor antagonism. Indeed, activation of HSC A_{2a}AR by extracellular adenosine markedly upregulates collagen secretion (26, 35, 36). Adenosinergic signaling, via A_{2a}AR activation, redistributes stress fibers and contractile capacity in HSCs (37), likely providing a

mechanism for a “stop” signal after cell migration, as evidenced by the observation that A_{2a}AR activation blocks the chemotaxis of HSC in response to platelet-derived growth factor (PDGF) (35). Finally, A_{2a}AR activation increased HSC TGFβ secretion (35) and decreased MMP expression (26). Since all of the mechanisms listed can be blocked by caffeine, blockade of pro-fibrotic adenosinergic signaling in HSC is a reasonable explanation for the antifibrotic effects of coffee.

According to the literature presented here, coffee consumption provides protection against liver fibrosis induced by well-established chemical models. The protective mechanism seems to be mediated primarily by the action of caffeine on HSC A_{2a}AR. However, there are holes in the literature that will need to be closed. First, since CCl_4 and other pro-fibrotic chemical agents require inflammation to induce fibrosis and cirrhosis, and multiple inflammatory cell types express adenosine receptors (38, 39), the observed effects may be mediated by changes in inflammatory cell function rather than those on HSC function. Second, the animal studies performed have taken only a cursory look at the relative importance of non-caffeine coffee constituents, in part due to methodological limitations. Lastly, animal models of fibrosis are themselves analogues of human fibrosis-to-cirrhosis progression, but they are not identical. Thus, it is very possible that animal models and studies in isolated HSC will prove useful to identify biological mechanisms, but the relevance to human health will be best tested in studies of human patients.

The progression of liver injury to fibrosis to cirrhosis is a slow but deadly process. The number of North American and European patients with chronic liver disease is increasing, primarily due to steady levels of hepatitis C infection but rapidly expanding levels of fatty liver disease (primarily non-alcoholic). Thus, identification of simple measures that can slow fibrosis and prevent cirrhosis in at-risk patients is critical. Since coffee consumption appears to have salutary effects on human health overall, coffee is an attractive lifestyle measure that patients can take.

Are we ready to “write a prescription for coffee”, as asked by Torres and Harrison in a recent commentary article? (1) Most likely, the answer is yes. Our rationale is as follows. First, there is sufficient evidence to provide biological plausibility for coffee as an anti-fibrotic. Second, coffee (for most individuals) is a pleasant addition to the diet, without profound adverse effects and possibly some other health benefits (again for most individuals). Lastly, other anti-fibrotic treatments are simply lacking; they are in the pipeline, but not yet available clinically.

However, we must face caveats as well. The human studies cited suggest that the most potent observed effects of coffee require the equivalent of four or more cups per day. We are not convinced that most individuals would easily tolerate this. Moreover, if we assume that the anti-fibrotic effects of coffee are mediated by caffeine, then should patients also be offered equivalent “doses” of tea, caffeinated soft drinks, or even caffeine pills? The latter two do not seem to be consistent with contemporary health practice, and probably for good reason. Thus, at present, we would suggest that any recommendations be limited to coffee (and for reasons cited above, limited to brewed coffee).

Hopefully, the most important effect gained by the observations reviewed here is not the use of coffee as a drug, but rather the generation of testable hypotheses as to the pathogenesis, prevention, and treatment of liver fibrosis and cirrhosis.

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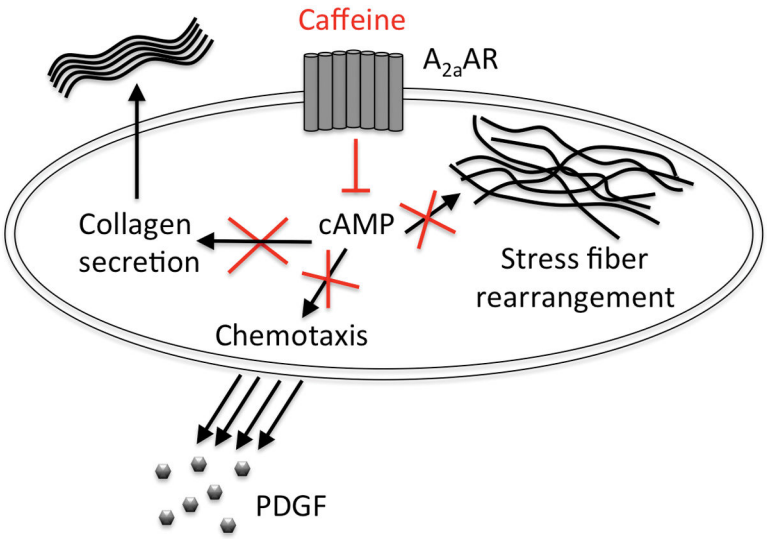

Figure 1. Proposed mechanism for the anti-fibrotic effect of caffeine in chronic liver disease

Caffeine is a known antagonist of the A_{2a} adenosinergic receptor expressed on activated hepatic stellate cells and other liver myofibroblasts. Stimulation of the $A_{2a}AR$ has several downstream pro-fibrogenic effects, including rearrangement of stress fibers, chemotaxis in response to PDGF and other stimuli, and secretion of fibrillar collagen, all of which may be inhibited by caffeine.