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Low, but not high, dose caffeine is a readily available probe for adenosine actions

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ABSTRACT

Caffeine is very widely used and knowledge of its mode of action can be used to gain an understanding of basal physiological regulation. This review makes the point that caffeine is – in low doses – an antagonist of adenosine acting at A_1, A_{2A} and A_{2B} receptors. We use published and unpublished data to make the point that high dose effects of caffeine are not only qualitatively different but have a different underlying mechanism. Therefore one must be careful in only using epidemiological or experimental data where rather low doses of caffeine are used to draw conclusions about the physiology and pathophysiology of adenosine.

1. Very many people habitually expose themselves to caffeine

Caffeine containing beverages are consumed all over the world. It can be estimated that the majority of adults are consuming, on a daily basis, caffeine in sufficient doses to have noticeable biological effects (Fredholm et al., 1999; Mandel, 2002). Caffeine is also widely consumed among children, albeit generally in smaller amounts (Ahluwalia and Herrick, 2015). Caffeine consumption as coffee is relatively easy to estimate as coffee is one of the most traded commodities (second after petroleum products according to official statistics, but it is not absolutely certain how this should be interpreted[1]). Tea is also a major traded product, but much of the tea consumed is in the countries where it is produced and levels of consumption is thus more difficult to glean from trade statistics (It has, however, been estimated by the International Tea Committee, an industry lobby group, that of the total market for hot drinks in the world that amounts to some 140 billion US $ tea comprises about 40.). The same is true for matte. Guarana, the fourth major plant source of caffeine (its seeds contain twice as much caffeine on a weight basis as coffee beans), is perhaps particularly used in energy drinks. These energy drinks together with caffeinated cola drinks constitute another major source of wide-spread caffeine consumption, whereas the amounts obtained from chocolate products are mostly insignificant.

The wide exposure of people from all ethnic groups to caffeine gives a possibility to use epidemiological methods to determine if caffeine has any major untoward or beneficial effects. Numerous such studies have been performed, and we will refer to some of the reviews of these studies rather than expand on the results here. Suffice it to say that in contrast to several early case control studies the majority of large cohort studies have failed to reveal major health hazards of coffee or tea consumption (Karlson et al., 2003; Higdon and Frei, 2006; Nkondjock, 2009; Santos et al., 2010; Welsh et al., 2010; Beaudoin and Graham, 2011; Je and Giovannucci, 2014; Gonzalez de Mejia and Ramirez-Mares, 2014; Ludwig et al., 2014; Zuchinali et al., 2016). Instead indications of beneficial effects in e.g. Parkinson's disease and type II diabetes

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[1] Mark Prendergast, who reported that coffee is the second most valuable traded commodity after petroleum products in his blog "Uncommon grounds" has since examined this again in a blog and concluded that it is probably a misinterpretation of statistics. What appears to be true is that coffee is the second most valuable commodity exported by developing countries. See http://www.thefreelibrary.com/Coffee+second+only+to+oil%3F+Is+coffee+really+the+second+largest...-a0198849799.

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have been documented (van Dam and Hu, 2005) see also Carlström this volume. There are also many typical effects upon single exposure including alerting effects of lower doses of caffeine (corresponding to one or two typical servings of coffee or tea) and the effects on sleep are well known and can of course be beneficial as well as detrimental (Clark and Landolt, 2016).

2. Caffeine produces biphasic effects

It is widely accepted that caffeine has biphasic effects, causing behavioral stimulation and some weak reward at lower doses, and anxiety, aversion, irritability and discomfort at higher doses (Mumford and Holtzman, 1991; Svenningsson et al., 1995; Kaplan et al., 1997; Fredholm et al., 1999). These effects limit the intake of caffeine containing beverages and it is, for example, possible that the higher intake of caffeine that occurs in schizophrenic patients could be related to the fact that in these patients caffeine is not anxiogenic (Hughes et al., 1998). Also in motivational terms lower doses are reinforcing, whereas higher doses produce aversion (Brockwell et al., 1991; Kuzmin et al., 1999). It can be noted in passing that the reinforcing effects of caffeine alone are not such as to induce self-administration (Briscoe et al., 1998). Caffeine is much less potent than e.g. cocaine in producing reinforcement and self-administration (Patkina and Zvartau, 1998), but it is able to prevent reinstatement of cocaine administration (Kuzmin et al., 1999).

These biphasic actions of caffeine are schematically illustrated in Fig. 1, which is somewhat modified from Fredholm et al. (1999). It also indicates that there appears to be rather considerable individual variations. Some of these appear to have a genetic background, and it seems possible that the two arms of the inverted U shape of caffeine dose-response are mediated by different mechanisms, which each show variability between individuals (Fig. 1b).

3. Effects of low doses of caffeine are mediated by adenosine blockade

The idea that the effects of methylxanthines such as theophylline and caffeine are due to blockade of the actions of adenosine rather than inhibition of cyclic nucleotide phosphodiesterases or promotion of calcium release from intracellular storage developed in the late 1970ies (Smellie et al., 1979; Fredholm, 1980). This concept is now well entrenched in pharmacological core knowledge. Hence it is not necessary to belabour it at length and we will only present an outline of the evidence.

Adenosine acts on four evolutionarily rather well conserved receptors denoted A_1, A_{2A}, A_{2B} and A_3 (Fredholm et al., 2001, 2011). They are 7-TM or G-protein coupled receptors, and as is so often the case among them the potency of the agonist depends on the receptor density. Thus, the higher the receptor number the more potent is adenosine (Fredholm, 2014). Another important basic fact is that already under basal conditions there is enough of the agonist around to activate the three most sensitive receptors, A_1, A_{2A} and A_3, provided they are locally abundant. Under more extreme physiological or pathophysiological conditions adenosine rises sufficiently to activate all types of receptors (Fredholm, 2014).

It is also well known, as noted above, that methylxanthines are inhibitors of adenosine action, except those actions that are mediated by A_3 receptors as these methylxanthines are almost 100 times less potent at that receptor than on the other three (Fredholm et al., 2001, 2011). Here it is also important to point out that caffeine is a less potent inhibitor of adenosine at its receptors than its two metabolites theophylline and paraxanthine (Fredholm et al., 1999, 2001, 2011; Svenningsson et al., 1999; Müller and Jacobson, 2011) The third primary metabolite, theobromine, is formed to a very limited extent in man and is a much poorer adenosine receptor antagonist than its parent caffeine.

4. High dose effects are not due to adenosine antagonism

The mechanism(s) underlying high dose effects of caffeine are less well known. There is an association between caffeine-induced anxiety and one genetic variant of the $A_{2A}R$ gene (Alsene et al., 2003), but not with several other variants (Rogers et al., 2010). The down-ward slope of the biphasic dose-response curve to caffeine remains in $A_{2A}R$ knockout (KO) mice even though the stimulatory effect was eliminated, and it was suggested that A_1 receptors may mediate the negative effects (El Yacoubi et al., 2000). However, this has later been shown not to be the case as these effects are seen also in A_1R KO mice (Halldner et al., 2004; Sturgess et al., 2010). Dopamine is critically important for conditioned place aversion to high dose caffeine (Sturgess et al., 2010), but this could be due to a role in learning the reaction rather than to unpleasant feeling(s). Using a microarray approach, we recently have identified three distinct patterns of gene expression induced by 50 mg/kg of caffeine: genes that are associated with the $A_{2A}R$ target, non-$A_{2A}R$ targets and the interaction between high dose of caffeine and non-

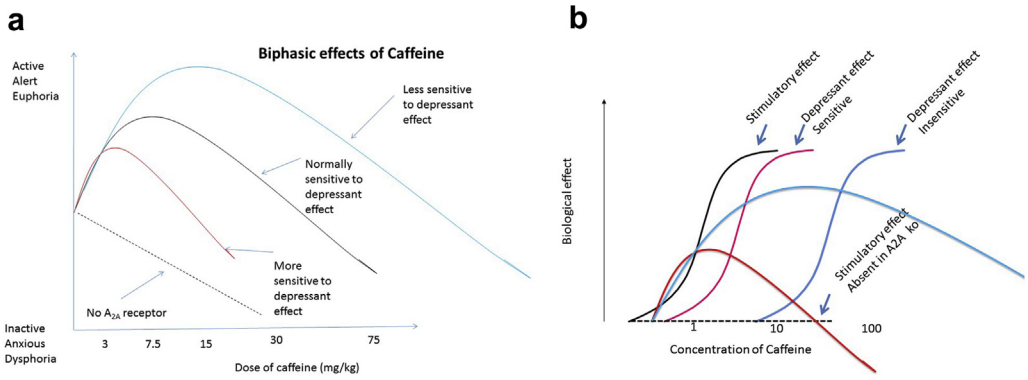

Fig. 1. Schematic representation of the biphasic response to caffeine, with low doses being generally pleasant and stimulatory and higher doses unpleasant or depressing. In Fig. 1a it is also indicated that there are major individual differences in the response. Some individuals start to experience the untoward effects at much lower doses than the majority, and some appear to have uncommon tolerance to these effects. Finally, we indicate that in animals that do not express the adenosine A_{2A} receptor the alerting effects are weakened or absent. Modified from (see also Fredholm et al., 1999). Fig. 1b tries to illustrate how differences in the sensitivity to the untoward effects will lead to differences in the magnitude of the positive effects. The figure is based on the idea that the positive and the negative effects are independent of each other because the underlying mechanism is different.