Coffee and opiate receptors

Another cup of coffee?

from Leslie L. Iverson

As writers, artists, scientists and anyone else who has to meet a deadline knows, the mild stimulant effects of coffee and even its ability to provoke anxiety and insomnia can be helpful. We all know that the stimulant effects of coffee are due to caffeine, and that this acts by inhibiting the enzyme cyclic nucleotide phosphodiesterase, thus enhancing the various effects mediated by this ubiquitous intracellular second messenger. Or that was what we thought we knew. In this issue of *Nature*, Boublik *et al.*[1] (p.246) report that coffee contains another potentially important psychoactive substance, and other recent results call for a radical change in our views of how caffeine and related xanthines act.

Boublik and colleagues report the startling discovery that solutions of instant coffee powder, both normal and decaffeinated, are able to inhibit the *in vitro* binding of ^{3}H-labelled naloxone and other ligands to opiate receptor sites in brain membranes. The active substance responsible for such effects can be extracted with ether, is of low molecular weight (1–3,500), dialysable, heat stable and resistant to peptidase degradation. The unknown material is currently being purified and its chemical identity will be awaited eagerly; it is clearly not caffeine, which is inactive at opiate sites. The partially purified material acted as an opiate antagonist, blocking the effects of morphine in the guinea pig ileum *in vitro*. The novel opiate material was present both in instant coffees and in coffee brewed from freshly roasted beans, but was not detectable in tea or in various other foods. Even more remarkable is that the opiate antagonist is present in substantial quantities; Boublik *et al.* estimate the concentration in a normal cup of coffee to be about five times higher that the IC_{50} for ^{3}H-naloxone displacement *in vitro*.

The question of how this might affect the coffee drinker has yet to be addressed. It is possible that the active substance is not absorbed or is rapidly metabolized, and thus never gains access to the nervous system. On the other hand, opiate antagonists such as naloxone have few if any detectable effects in normal subjects. When given in a blind manner, normal subjects are unable to determine whether they have received naloxone or placebo[2]. It is thus possible that coffee drinkers are unwittingly exposed to opiate receptor blockade, although it is not clear how this may contribute to the overall effect.

It remains more likely that the stimulant actions of coffee do result from the substantial amounts of caffeine consumed — about 100 mg per cup. Recent findings point to cellular receptors for adenosine, rather than phosphodiesterase, as a likely target for caffeine and other psychoactive xanthines[3,4]. It has been known for some time that caffeine and related methyl xanthines (for example, theophylline) can antagonize the effects of adenosine on a variety of tissues, and this now seems a more likely mechanism of action than the very weak inhibitory effects which these compounds exert on cyclic nucleotide phosphodiesterase. There is increasing interest in the possible role of adenosine as a modulator of various cellular responses to hormones and to neurotransmitters[5,6] as part of a general focus of interest on purines as possible chemical messengers or modulators[7].

Adenosine receptors in brain membranes have recently been identified by *in vitro* binding techniques, using the stable analogues 2-chloroadenosine[8] or N^6-cyclohexyladenosine[9] as radioligands. The latter compound proved to be a potent behavioural depressant when administered to mice[10], and a good correlation was found between the potency of caffeine and other xanthines to stimulate behavioural activity and their potency in inhibiting the binding of ^{3}H-cyclohexyladenosine to brain membranes *in vitro*.

Both lines of research on the psychopharmacology of coffee raise many unanswered questions. The possibility that coffee drinkers regularly imbibe an opiate receptor antagonist reminds us of how little we understand of the normal functioning of the endogenous opioid mechanisms. Does the lack of effect of opiate antagonists in normal subjects mean that these systems are used only *in extremis* — in conditions of stress or pain? If caffeine acts by blockade of adenosine receptors in brain, what function do such receptors normally have, and where does the adenosine come from? In seeking the answers to such questions many more cups of coffee will certainly be needed. □

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Pacific volcano statistics

How many ocean volcanoes?

from Peter J. Smith

Geologists have known for decades that there are thousands of dead and alive volcanoes on the ocean floors, but they have never been too sure what to make of most of them. The few volcanic islands and seamounts in linear formation and with an age progression along each chain have recently attracted attention as 'hotspot volcanoes' and have become vaguely assimilated into the plate tectonic story; but the majority, apparently unrelated individual features, have hitherto often been regarded as of little general significance. It is probably fair to say that the volcanic pimpling of the oceanic lithosphere has been seen largely as a curiosity with only marginal, if any, relevance to global tectonics.

But that view may be quite wrong, as a simple statistic derived by Batiza suggests (*Earth planet. Sci. Lett.* **60**, 195; 1982). Batiza has examined all 12,000 seamounts and volcanic islands shown on bathymetric charts covering most of the Pacific and concludes that they account for about 5 per cent by volume of the oceanic volcanic layer. Moreover, bearing in mind that the bathymetry of much of the Pacific floor is not fully known and extrapolating from those areas surveyed in detail, it becomes clear that the true number of volcanoes in the Pacific could be as high as 55,000. In other words, anything up to 25 per cent of the oceanic lithosphere could be accounted for not by the near-horizontal sheet usually envisaged but by the volcanic features superimposed upon it.

That rather changes the conventional perception of seamounts' importance, for 25 per cent is no insignificant proportion. On the other hand, the statistics on current activity are rather less impressive. Batiza estimates that about 3 per cent of oceanic volcanoes are active, accounting for only about 4 per cent of the total volcanic production from seamounts and oceanic ridges together. Unfortunately, little is known about the internal compositions of seamounts because drilling has not completely penetrated one; but if the chemistry of seamounts turns out to be vastly different from that of ridge-generated material, even the 4 per cent that oceanic volcanoes represent could have a profound influence on bulk lithospheric composition.

So with the possibility in mind that a