

Neurochemical Effects of Caffeine and Behavioral Tolerance to Caffeine

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Caffeine is known to produce biphasic; behavioural effects - lower doses being stimulatory, higher doses being inhibitory. Tolerance rapidly develops to these effects. Of all the potential biochemical targets for the actions of caffeine the only one to be activated at the levels of caffeine during normal consumption of caffeine is antagonism of the actions of the endogenous adenosine at A1 and A2a receptors, the latter ones being more sensitive to low doses of caffeine than the former ones. A1 receptors are abundantly expressed – especially at the terminals of excitatory nerve endings. When the actions of adenosine are blocked at these sites transmitter release, especially glutamate release, is increased. This will affect the activity of neurones in the striatum known to regulate motor behaviour and motivational aspects of behaviour. The latter structure contains both A1 and A2a receptors. Adenosine A2a receptors are virtually confined to the striatal GABAergic neurones where they are colocalized with dopamine D2 receptors. In the same structure adenosine A1 receptors are colocalized with dopamine D1 receptors. The blockade of A2a adenosine receptors by caffeine appears to be crucial for the stimulatory effects of caffeine.

Locomotor tolerance to caffeine in rats is not reflecting an increased metabolism of the methylxanthine. Although the mechanisms responsible for this tolerance do not develop to a pure adenosine A2a antagonist and remain to be further explored, tolerance to the motor stimulant effects of caffeine is accompanied by a decreased expression of adenosine A2a receptors in the anterior parts of the striatum and an increased expression of the adenosine A1 receptor gene in the amygdala.