

# [Therapeutic effects and uses of caffeine](https://assignbuster.com/therapeutic-effects-and-uses-of-caffeine/)

Abstract

Caffeine which is part of many beverages like tea, coffee, energy drinks, cola drinks and chocolates is one of the widely used stimulants by the human population all over the world. The consumption of caffeine varies across age groups. Generally adults follow a pattern in the consumption related to the time of the day, the sleep-wake cycle and other behavioral attributes. Caffeine acts as adenosine A 2A receptor antagonist and the blockage of these receptors in striatal basal ganglia is said to be the cause of the stimulant effect of caffeine. Apart from the stimulant and subtle motor effects, caffeine also has several therapeutic effects in relation to its cellular mechanism. Caffeine is said to have neuroprotective properties and can be used as a drug in the treatment of Parkinson’s disease. Caffeine can protect cells from skin cancer resulting from UV radiation since it is able to induce apoptosis of tumorigenic cells. Caffeine therapy was found to be effective in relief from apnea of prematurity in infants. When combined with PTEN treatment, caffeine has a synergistic effect in inducing the apoptosis of human colorectal cancer cells. Caffeine can also help in alleviating of Post dural puncture headache (PDPH). There is a lot of scope to develop caffeine as a potent therapeutic drug and as part of other combinatorial therapies.

Introduction

Caffeine is used as a recreational beverage in the form of coffee as well as a potent stimulator in form of energy drinks in all the parts of the world. Caffeine is a form of methyl xanthine and chemically it is 1, 3, 7-trimethyIxanthine. This stimulates the CNS.

Based on the action of methylxanthines, 3 possible theories have been proposed regarding why does caffeine have effect on the CNS. Earlier it was thought that the effect of caffeine is due to the rise in levels of cyclic AMP, as caffeine inhibits the enzyme cAMP phosphodiesterase. (1) Also, caffeine may lead to release of Calcium ions from ER and lead to a rise in calcium ions in skeletal muscles. (2) However the most promising theory seems to be that caffeine inhibits adenosine by acting as antagonists to adenosine receptors. (3) To find out which mechanism is the most suitable to explain the action of caffeine, some factors were considered. Caffeine was found to be more potent in the inhibition of adenosine receptors than in the inhibition of cAMP phosphodiesterase. Also, for the release of calcium ions in the skeletal muscles and to observe motor effects, very high concentrations of caffeine would be required. (4)Thus the action of caffeine is attributed mostly to inhibition of adenosine receptors.

Regarding the effective concentration of caffeine , the caffeine concentration in plasma is usually below 100 µM after ingestion of caffeine-rich beverages like coffee etc. However, to observe toxic effects like tachycardia and anxiety, the concentration should be above 200 µM in the plasma.

Cellular Mechanism of Caffeine

Striatal membrane of basal ganglia adenosine A 2A receptors lead to reduction in the affinity of D2 receptors for agonists. (5) But also, apart from this, A 2A receptors lead to an increase in cAMP production whereas D2 receptors causes a decrease in the production of cAMP. These antagonistic relationships affect striato-Gpe neurons which cause the indirect pathway. The biomarker used to assess the activity of striato-Gpe neurons is enkephalin mRNA in mice studies. Thus caffeine acts against the A 2A receptors, which in turn affects the dopamine D2 receptors increasing the motor activity. But some studies suggest that the dopamine D2 receptors may not be involved and the A 2a receptors alone can cause the influence on motor activity. (6)

Caffeine counteracts against fatigue during exercise. This happens due to the blockade of A 1 receptors , and thus in turn leads to increase in dopamine concentration. Caffeine does not act on the ventral striatum.

Generally the blockage of A 2a receptors are more important in relation to the stimulant effect of caffeine. This was proved by the use of knockout mice in which A 2A receptor had been knocked out. DPCPX (1, 3-dipropyl-8-cyclopentylxanthine) was used, which is antagonist for A1 receptors. After the administration of caffeine a lower locomotor activity was noticed in comparison to wild type mice.

To study the role of dopamine in the action of caffeine, reserpine and also D1 and D2 receptor antagonists were used was used to study the effect

Thus caffeine acts on striato-Gpe pathway and caffeine acts as an adenosine A 2A receptor antagonist. The levels of addiction to caffeine is a matter of discussion since there is almost no tolerance to the adenosine A 2A receptors. So the withdrawal symptoms of caffeine may be linked to blockade of A 1 receptors. (5)

Caffeine consumption by human population

People across the world consume caffeine in the form of various beverages, like tea and coffee, cola drinks, chocolate and energy drinks . A statistical study was conducted in 500 adults of Italian origin ( about 280 males and 300 females). Caffeine intake and other factors ( like smoking cigarettes along with caffeine consumption) were studied. It was found out that males had higher amount of caffeine in a day as compare to females. In this study, the work pattern of the sample population hasn’t been considered. About the time of the day most (about 90%) of the people had caffeine in morning and afternoon and mostly in the form of tea and coffee. The time of the day and the sleep-waking pattern also influences caffeine intake which has been called as “ morningness” and “ eveningness” according to the time people woke up and had coffee/tea. The lesser forms of caffeine intake comprised of cola drinks, chocolate and energy drinks. Smoking of cigarettes was linked to caffeine consumptions as a higher number of smokers had much more caffeine intake in comparison to non-smokers. (7)

Therapeutic Effects of caffeine

Caffeine and Parkinson’s disease

Parkinson’s disease is one of the most common neurodegenerative disorder which results in degeneration of neurons of the basal ganglia and other disturbances like tremors, rigidity, bradykinesia generally in adults above the age of 45 years. The current therapy involving levodopa is not effective at the efficacy reduces with time and it is also associated with side effects. The biomarker for the efficacy of the therapy is the induction of motor activity on the lesion side which is in turn due to dopamine transmission. Since caffeine acts as an adenosine A 2A receptor antagonist, further investigation is possible to develop caffeine as an anti-parkinson’s drug. (13) However suitable measures need to be taken to prevent side effects like anxiety and cardiovascular effects. Caffeine also has neuroprotective properties and ability to reduce glutamate toxicity. (5)

Caffeine prevents skin cancer

The topical or oral application of caffeine is found to destroy UV damaged keratinocytes. This is according to a study carried out on mice. Caffeine augments the apoptosis of UV damaged keratinocytes of the skin and , can have applications in preventing skin cancer. This study is significant because the anti-cancer properties of caffeine were already studied based on papers (1986 Jacobsen et al, 2007 Abel et al.). Regarding the cellular mechanisms , it was found out none of the known mechanisms like effect of caffeine on cyclic AMP levels etc., contribute to this effect . One of the mechanisms is the inhibition of ATR, which was found out based on in vitro and in vivo studies. ATR also targets checkpoint kinase 1 (Chk1), which also gets inhibited. Also, p53 mutant skin cells were used to conclude that p53 gene does not have any effect in this pathway. The future prospects of this study can be to include caffeine in sunscreen applications to reduce skin damage by UV light and as potential skin cancer preventing medicine. (8)

Caffeine therapy in Apnea of Prematurity

Apnea which occurs at prematurity is the difficulty and then subsequent stoppage of breathing which occurs in infants who do not complete their gestation period and are born at less than 34 weeks. Caffeine was found to reduce the intensity of apnea and the rate at which it happens. Also, it negates the need for mechanical ventilation in the initial week of the therapy. Caffeine citrate injections were given to about 2006 infants , and parameters like birth weight etc. were measured to find out the effect of caffeine on bronchopulmonary dysplasia . (9) These experiments were done and compared with placebo studies. Also, according the study by the author along the same lines, when premature infants were treated with caffeine therapy, the incidence of cerebral palsy and cognitive delay was reduced. (10)

PTEN Treatment combined with caffeine

We have already seen that caffeine can destroy cells whose DNA has been damaged by effects such as UV radiation. It is also seen that caffeine can destroy cancer cells also by enhancing the effect of anti-cancer agents. This is the apoptotic effect of caffeine on cancer cells, which is carried out by inhibition of ataxia-telangiectasia-mutated (ATM) and ATR kinase (Rad3-related) activity at cell cycle check points. Thus if caffeine is combined with other anti-cancer agents, it can help in enhancing their effect. Many studies have been conducted regarding the effect of PTEN ( tumor suppressor gene located in chromosome 10). PTEN is said to suppress tumor and cellular proliferation of cancer cells by arresting the cell cycle at G1 . When a combined application of caffeine was given along with PTEN , it created a synergistic effect and lead to apoptosis of cancer cells of human colorectal cancer. But it did not have any effect on normal cells. Thus this can be an effective combinatorial therapy to destroy tumorigenic cells. (11)

Caffeine based therapy in Post dural puncture headache

Caffeine can help in alleviating of Post dural puncture headache (PDPH). A study found out that about 300mg of an oral dose of caffeine can significantly help in the treatment of PDPH in the early stages. Also, it mentioned that oral form of caffeine therapy is more safe and efficacious in the treatment of PDPH. (12)

Future Directions

All of these findings state that caffeine is a potent drug which has a lot of physiological effects on our body. It is entirely safe to consume in moderation since the concentration in plasma of caffeine is usually below 100 µM . When used as a form of therapy or with other drugs as a combinatorial treatment, caffeine can have many therapeutic effects. Thus the future work can be in medical research related to caffeine.

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