REVIEW ARTICLE

Effect of Caffeine in Genetic and Cancer

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Summary

Caffeine is one of purine compounds which occur naturally in different species of plants such as: tea, coffee and cacao plants. DNA synthesis and replication are affected by caffeine through different methods and these will lead to exhibition of more than one effect in cell division. Caffeine has not proved to have a mutagenic effect, but it prevents the action of mutagenic compounds. Harmful activity of UV is blocked by caffeine when it is added to the treated cells with UV light. Furthermore, caffeine is not found to have a chief role in the conversion normal cells to cancer state, but, in fact, it has a reflexive action when it prevents the carcinogenic compounds to effect on cell division.

الخلاصة

يعود الكافئين إلى مجموعة مركبات البيورين حيث يتواجد بصورة طبيعية ضمن أنواع مختلفة من النباتات مثل الشاي والقهوة والكاكاو, ويؤثر الكافئين على تخليق وتضاعف الحامض النووي DNA والذي بدوره يؤثر على عملية الانقسام الخلوي.

أما من ناحية تأثير الكافئين على إحداث الطفرات فلم يثبت كونه مطفر للخلايا وإنما على العكس وجد بأنه يمنع فعل المركبات المطفرة, ومن الفعاليات الأخرى للكافئين هو إيقاف التأثير المدمر للأشعة فوق البنفسجية UV في الخلايا المتعرضة لها, ولم يلاحظ للكافئين أي دور رئيسي في تحول الخلايا الطبيعية إلى خلايا سرطانية وإنما وجد بأنه يمنع تأثير المركبات المسرطنة .

Caffeine and genetic

Caffeine, 1, 3, 7-trimethylxanthine, occurs in coffee, tea, cacao, kola and mate [1]. It is used as central nervous system stimulants. Caffeine connected with many genetic activities in the living cells which make it more important compound in the field of cancer diseases. Cell division in the living organisms, in genetic review, is inhibited by caffeine e.g. inhibition of DNA synthesis in *E. coli* K2. This inhibition could be explained by two suggested mechanisms. Firstly: Inhibition of ATP dependent enzymes e.g. DNA helicase and DNA poly III and by this mechanism, caffeine increased the activity of known DNA inhibitors antibiotic e.g. Actinomycin, Novabiocin, Nalidixic acid and Thymidine [2].

Secondly: intercalating of thymidine within DNA is inhibited when *E. coli* cultured in the media containing caffeine before adding thymidine as result from inhibition of thymidine kinase, whereas this activity decreased in the case of addition caffeine before thymidine in the culture media [3].

The inhibitory effect of caffeine on the DNA synthesis is also studied in mammalian organism. Caffeine stimulates the mitosis of mammalian cells to begin before completed DNA replication in the S phase of cells and it could be related to many events including, aggregation of immature chromosome, disruption of nuclear membrane and shaped rounded cell. Caffeine also stimulates the translation of RNA with save the producing proteins with each other in the S phase of cell division after inhibition of DNA synthesis [4].

In plant cells, 1-10 mM of caffeine caused chromosomal aberration in the generating cells at G2 phase of *Allium cepa* in tissue culture [5]. High concentration of caffeine cooperated with some antifungal compounds e.g. bleomycin and mitomycin C to inhibit the second stage of meiosis in the *Saccharomyces cerevisea* [6].

Caffeine and mutagenesis

The direct effect of caffeine on DNA is represented by parallel attachment with nitrogen base without intercalating within the strand of DNA, in contrast with caffeine derivatives which strongly have the ability to intercalating with these strands [7]. This intercalating of caffeine with DNA dose not make it as mutagenic compound [8], but it prevents the other mutagens [9] e.g. 2 mg/L of caffeine blocked the mutagenesis activity of nine compounds out of ten with variation in the blocking effect between high, medium and low effect [10].

The preventing of mutagenesis process by caffeine could be explained by reducing exonuclease activity to basal level after prevents x-Mre11 phosphorylation [11] or through inhibition of phosphatase transferase (one of protein kinase components) which is responsible for activities of ATM (ataxia-A-T related) and ATR (telangiectasia mutated) mutants [12]. Caffeine could become mutagen at high concentration as noted when compared between the effect of theophylline and high concentration of caffeine on the *B. subtilis*. It was found that caffeine stronger than theophylline to become mutagen, especially after 10 minutes of germination of bacterial spore and this effect was reduced by adenosine [13]. Maté, drink similar to tea, containing 3 mg/L of caffeine is tested for mutagenesis ability in *S. cerevisiae*. The result revealed that it is not mutagen, but same concentration of pure caffeine may form a mutant from the type of spontaneous mutation [14].

Caffeine prevents UV damage

Caffeine has the ability to affect different activities connected with DNA. This phenomenon makes caffeine to be used in the inhibition or prevention of the damage of harmful rays, especially UV by different mechanisms. One of these mechanisms is prevention of DNA repair [15] of DNA strand in attacked living cells by harmful rays e.g. adding of caffeine to the cell containing plasmid DNA (PBR 322) when attacked by gamma rays will block the repair of plasmid DNA through the effect of caffeine on the repair enzymes, while adding caffeine before rays attack or during the period of attacking will protect the cells as result from intercalating of caffeine with radical ions (O^{-2}, ROO and H2O2) to prevent the harmful effect of them [16]. The inhibitory effect of caffeine on DNA repair depended on its effect on ATM and ATR kinase. Daniel et al showed that caffeine treatmentcauses a dose-dependent reduction in the total amount of HIV-1 and avian sarcoma virus retroviral vector DNA that is joined to host DNA in the population of infected cells and also in the number of transduced cells [17].

The blocking of DNA repair in mammalian cells is studied. Repair operation in attacked tissue culture of human and mouse cells by UV is not completed when treated with caffeine, whereas untreated cells are cured from the damage of UV after 12 hours [17].

It is noted that caffeine, in other few studies, aids UV light to become harmful.1 mM of caffeine makes change in sister chromosome, especially at the first and second stage of cell cycle [20] and its work is believed on the S and G2 stage [4].

Caffeine and cancer

The role of caffeine and food containing caffeine as causative agent of cancer disease is not determined in many types of cancer e.g. lower urinary tract cancer, pancreatic cancer, breast cancer or fibrocystic breast disease, ovarian cancer and large bowel cancer [19] and the same result is appeared in the case of breast cancer after observing 1271 women consumed approximately 4 cups of coffee per day [20].

The effect of caffeine on the increase or decrease of development of malignant cell at cellular and molecular level is dependent on the host cell type and the type of carcinogenic compound used with it [19]. Caffeine prevents cells to become cancer cell by performing many activities:

1- Enhancement the first step of DNA replication in cells treated with carcinogenic compounds before transformed to cancer cells [21].
2- Prevention the development of cancer cells by increasing the intracellular cAMP concentration e.g. inhibition of the initiation and development of malignant and benign thyroid cancer [22].
3- Blocking cancer cell growth via the inhibition of DNA repairing and replication [9, 23].
4- Increasing the differentiation of undifferentiating cancer cells and this will be decreased the growth of cancer cells as noted with breast cancer when treated with caffeine or coffee [20].

Caffeine also could be used as assistant of many anticancer drugs to do their curative action. The 2 mM of caffeine enhance the efficiency of CDDP compound for treatment of cancer disease e.g. osteosarcoma by preventing repair of DNA with vanishing of the side effects that resulted when CDDP drug is used alone and it is preferable to have caffeine or coffee after having CDDP and not with or before [23].

The assistant of caffeine is also noted in the case of drugs against sarcoma when four states of those drugs lost their damage action on DNA beside of increase their effect [24].

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