

PERSPECTIVES

The perspective of caffeine and caffeine derived compounds in therapy

Pohanka M^{1,2}

Faculty of Military Health Sciences, University of Defence, Hradec Kralove, Czech Republic.
miroslav.pohanka@gmail.com

ABSTRACT

Caffeine (1,3,7-trimethylxanthine) is a plant secondary metabolite with a significant impact on multiple processes and regulatory pathways in the body. Though major part of the population meets caffeine via coffee, tea or chocolate, it has also an important role in pharmacology and it is used as a supplementary substance in medicaments. Currently, the ability of caffeine to ameliorate some neurodegenerative disorders is proved in some studies. This review describes basic data about caffeine including toxicity, pharmacokinetics, biological mechanism of the action, and metabolism. Beside this, promising applications of caffeine, new medicaments and derivatives are discussed. Relevant papers and inventions are depicted in the manuscript.

Caffeine is a pharmacologically promising substance that deserves big consideration in the current research and development. The compound has several reasons to be an object of scientific interest and to be used for pharmacology purposes. Despite an extensive research for a long time, no significantly negative effects on human health were proved hence caffeine can be considered as a completely safe compound. The recent data about amelioration of neurodegenerative and other disorders are promising and deserving more work on the issue.

ARTICLE HIGHLIGHTS

Caffeine is a purine alkaloid from plants and it has a broad use in current pharmacology.

Caffeine is a competitive antagonist of neurotransmitter adenosine on adenosine receptors.

The substance is added as a supplementary to drugs and food.

Besides interfering on adenosine receptors, caffeine interacts with acetylcholinesterase, monoamine oxidase, phosphodiesterase, ryanodine receptors and others.

Current research is devoted to the role of caffeine in neurodegenerative diseases and immunity alteration.

New chemical compounds based on caffeine moiety are prepared (Tab. 4, Fig. 6, Ref. 149). Text in PDF www.elis.sk.

KEY WORDS: caffeine, Alzheimer disease, Parkinson disease, immunity, adenosine, GABA, dopamine, theophylline, theobromine.

Introduction

Purine alkaloids have a significant role in pharmacology and food chemistry. Caffeine, 1,3,7-trimethylxanthine, is probably one of the most relevant purine alkaloids in this point of view. Coffee, a caffeine containing beverage prepared from plants *Coffea arabica* and *C. canephora*, have been known since medieval time (1). Caffeine can be found in tea plants like *Camellia sinensis*, so humans probably use caffeine containing beverages for more than four thousand years since drinking of tea was documented in ancient times (2–4).

Production and sale of coffee seeds belongs to the significant income of developing countries. The expected economic profit from the agriculture of caffeine plants is around 20,000 USD per year and hectare (5). Planting *C. sinensis* for tea leaves production have similar importance in the agriculture as planting caffeine plants (6). Caffeine has an eminent role in pharmacology as well. The fact is eminent from the citations and the following text (7–9). Pure caffeine can be quite easily obtained by an extraction from coffee seeds or tea leaves (10,11) and chemical synthesis is applicable as well (12,13).

Because caffeine exerts low toxicity combined with relevant biological effects, it is an object of interest for many investigators. Caffeine is a stimulating compound acting via adenosine receptors; however, the other neural pathways can be also involved in caffeine effect. Broad implication and a promising use of caffeine can be learned from the current literature. In this review, caffeine is introduced as a simple alkaloid able to modulate many pathways in the body. However, major effort was given to discussion about caffeine's pharmacological importance and the opportunity to use caffeine in combination with the other biologically active compounds or use of the caffeine derivatives. Targets for caffeine, its metabolism and toxicology are

¹Faculty of Military Health Sciences, University of Defence, Hradec Kralove, Czech Republic, and ²Department of Geology and Pedology, Mendel University in Brno, Brno, Czech Republic

Address for correspondence: M. Pohanka, MD, Faculty of Military Health Sciences, University of Defence, Trebesska 1575, CZ-500 01 Hradec Kralove, Czech Republic.

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discussed here as well and the expected directions of next research are proposed.

Biological synthesis, metabolism and pharmacokinetics of caffeine

Caffeine is a purine alkaloid and the anabolism of caffeine has steps identical or similar to the anabolism of many other alkaloids.

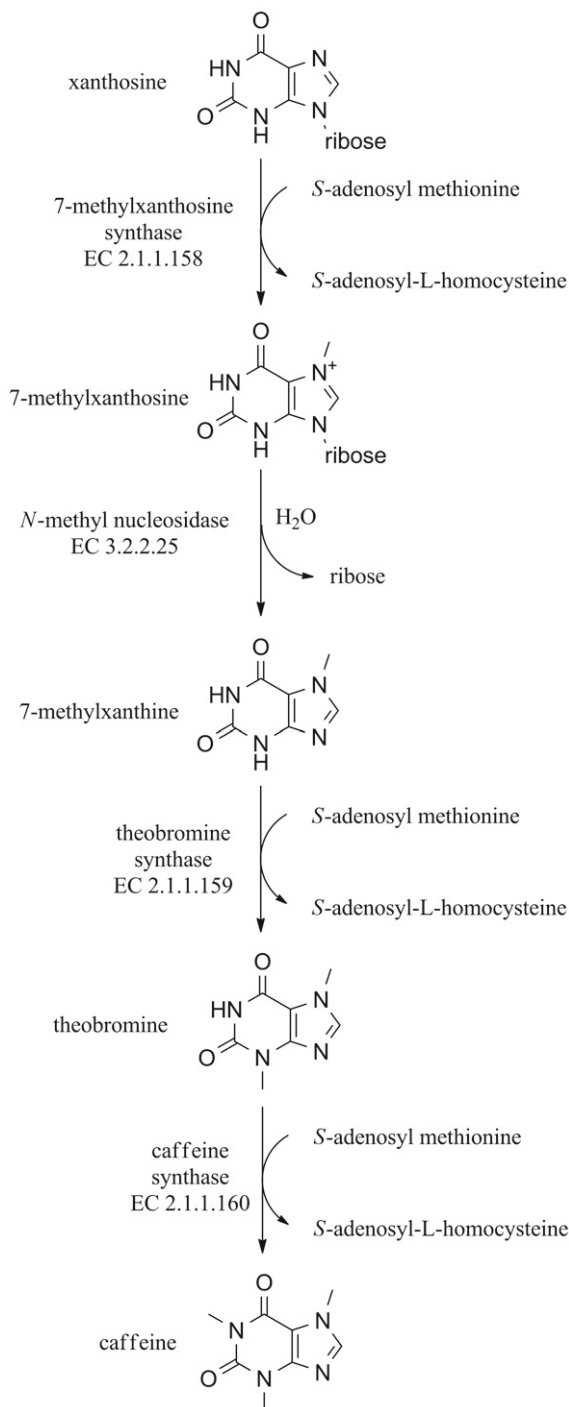


Fig. 1. Synthesis of caffeine in the plants.

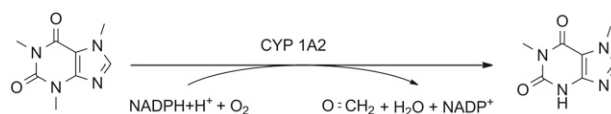


Fig. 2. Caffeine demethylation to paraxanthine.

Pathway for caffeine remained unrevealed for a long time and some doubts about caffeine precursor in plants were claimed until resolving the issue in the recent years (14). Dominant pathway of caffeine production in the plant is based on consequent methylation in xanthosine, 7-methylxanthine and theobromine (15,16), and hydrolysis of ribose from 7-methylxanthosine by N-methyl nucleosidase (EC 3.2.2.25) (17,18). S-adenosyl methionine is a source for implementation of the methyl moiety into the intermediates and it is also a co-substrate for the involved enzymes 7-methylxanthosine synthase (EC 2.1.1.158), theobromine synthase (EC 3.2.2.25), and caffeine synthase (EC 2.1.1.160) (19). Caffeine biosynthesis pathway is summarized in the Figure 1.

Typical intake of caffeine is peroral and drinking of caffeine containing beverages or food is probably the most relevant in the current population. Intake of caffeine in drugs is another significant income of the compound. The peak concentration of caffeine in plasma is reached in 120–180 minutes after its intake; however, fasted people can have reached caffeine peak in plasma within 60 minutes as proved on male volunteers (20). The half time of caffeine in human plasma is 5.7 h and the clearance is 0.74 ml/min×kg (21). However, the authors proved that the half time can be dramatically increased up to nearly 15 hours when liver function is impaired e.g. due to cirrhosis. It should be emphasized that caffeine is metabolized in the liver as mentioned further. The metabolic products are biologically active as well and their effect is very close to the effect of caffeine (22). In literature, another half time for caffeine can be found. In an example, half time 4.3 h for a healthy population and even 3.0 h for smokers were reported by Seng and co-workers (23).

In mammals, caffeine is metabolized by cytochromes P450 via oxidative demethylation into paraxanthine, theobromine and theophylline. The methyl moiety is split from the structure as formaldehyde (24). The most relevant pathway for caffeine detoxification is based on oxidative demethylation by P450 isotype CYP1A2 to paraxanthine (25,26). Activity of CYP 1A2 is distinct in the population and forms such as 1A, 1B, 1C, and 1F can be found among humans; however, the ability to oxidize xanthine alkaloids is not significantly different (27,28). The oxidative demethylation of caffeine to paraxanthine is depicted in the Figure 2. Beside CYP 1A2, other isotypes can be also involved in the oxidation of caffeine. Namely, CYP 2C8, CYP 2C9, CYP 3A4 in humans and 2C11 or 3A2 in rats play a role in the metabolism (29). As aforementioned in the work by Mesáros and co-workers, the metabolism of caffeine is significantly depressed in liver when hepatitis occurs (21). On the other hand, caffeine plausibly reduces inflammatory processes in liver during the hepatitis (30,31). Though beneficial effect of caffeine in patients who suffered from hepatitis can be learned from the quoted papers, more work on the issue is needed to make conclusions and to understand mechanism of the effect. Involvement

ment in regulation of immunity response can be mentioned as an hypothesis how caffeine can be implicated in change of the diseases progression (32).

Interaction of caffeine with receptors and other target structures

Caffeine has the major pathway in the body where it takes its biological effect. It is a competitive antagonist of neurotransmitter adenosine on adenosine receptors. Adenosine is an important neurotransmitter interacting with the adenosine receptors (33). There are four known types of adenosine receptors designated as A_{1} , A_{2A} , A_{2B} , and A_{3} being coupled to G protein and responsible for e.g. regulation of the heart rate, vasodilatation, bronchospasm, smooth muscle contraction, inhibition of neutrophils degranulation with an effect on adjacent immunity and some others (34–36). Themental sedation because of receptor A_{2A} and bradycardia via receptors A_{1} as well as A_{3} are typical manifestations of agonism and the oppose effect is evoked just by caffeine(37,38). The A_{3} isotype is also involved in the regulation of neutrophils and its degranulation (39,40). From the mentioned receptors, the isotype A_{2A} is dominantly located in central nervous system, especially in the extraatrial forebrain, where it acts on behavior and mental excitation in a link to dopamine, glutamate and brain derived neurotrophic factor signaling (41–44). In recent time, neuroprotective effects of antagonist on A_{2A} receptors after cerebral ischemia were discovered (45). Cerebral ischemia is considered as a consequence and maybe the primary reason for some neuropathologies with unknown etiology, antagonism on the receptors by caffeine or any other compound would have significant pharmacological sense. Beside the aforementioned effects, adenosine is responsible for bronchospasm, which is regulated through A_{2B} receptors (46). In the bronchus, caffeine can suppress bronchospasm and even significantly ameliorate bronchoconstriction just by antagonizing of the A_{2B} (47,48). When we take a global look at the adenosine receptors, it should be emphasized that other xanthines structurally close to caffeine are also antagonists on adenosine receptors (49,50). Theophylline as an example (51).

Beside the adenosine receptors, caffeine acts also on other neurotransmission systems, but the effect is significantly lower and probably is a consequence of the effect on adenosine. Imbalances in acetylcholine, epinephrine, norepinephrine, serotonin, dopa-

mine and glutamate after caffeine administration are described in the current literature(52–56). On the other hand, caffeine can have targets in the pathways since most of the data proved in laboratory on animals have not been studied on an in vitro model. Detailed data about the role of caffeine in the pathways are scarce and conclusion has to be inferred from available sources. The idea of multi-target effect of caffeine is confirmed by some works where the targets were revealed.

The effect on dopamine neurons can be caused by a reversible inhibition of monoamine oxidase, which seems to have small scale, but significant enough to be demonstrated in the body (57). This inhibition can protect from the oxidation of epinephrine, norepinephrine, serotonin, and dopamine, hence research on the issue has a pharmacological importance and enhance the current knowledge about caffeine(58). Cholinergic system is altered by caffeine via inhibition of the enzyme acetylcholinesterase. Caffeine acts as a non-competitive inhibitor of the enzyme and protect thus from splitting of neurotransmitter acetylcholine, which may result in a higher accessibility of acetylcholine on acetylcholine receptors(32,59). Cholinergic system is an important part of the both central and peripheral nervous system with wide functions(60–62). Cholinesterases are widely presented in the blood as well (63). A link to the immunity system via cholinergic system by cholinergic anti-inflammatory pathway can be another target of caffeine (32). Besides the aforementioned extracellular signaling, caffeine has also its targets in intracellular signaling pathways. Intracellular messengers cAMP and cGMP have a protracted time for signaling in the presence of caffeine because of the reversible inhibition of phosphodiesterase (64,65). The second effect of caffeine on intracellular pathways is mediated through ryanodine receptors located on sarcoplasmic reticulum and serving as specific channels for the influx of Ca^{2+} (66–70). Caffeine is a full agonist on the ryanodine receptors and it forces Ca^{2+} transient (71–73) also it is used as control in experiments where Ca^{2+} should be transferred to cells (74). It has also an impact on the genetic information via poly(ADP-ribose)polymerase-1 that is activated and responsible for DNA strand breaks repair. Caffeine acts as an inhibitor of the enzyme (75). The effect results not only in an alteration in DNA repair, but also in cell cycle control (76,77). The meaning of caffeine ability to inhibit poly(ADP-ribose)polymerase is not fully explored. Though some apprehensions that caffeine would initiate cancer were stated in the past, clinical tests either did not confirm

Tab.1. Molecular targets of caffeine.

Target structure	Role of the target structure	Effect of caffeine	References
Acetylcholinesterase	it splits neurotransmitter acetylcholine	non-competitive inhibitor of acetylcholinesterase	(32,59–62)
Adenosine receptors	G protein coupled receptor mostly implicated in sedation (bradycardia, suppression of mental excitation etc.)	competitive antagonist on adenosine receptors	(37–44,47,48)
Monoamine oxidase	oxidizes epinephrine, norepinephrine, serotonin, and dopamine	reversible monoamine oxidase	(57,58).
Phosphodiesterase	the enzyme hydrolyzes secondary intracellular messengers cAMP and cGMP	reversible inhibitor of phosphodiesterase	(64,65)
Poly(ADP-ribose)polymerase	DNA repair, apoptosis	reversible inhibitor of poly(ADP-ribose)polymerase	(75–77)
Ryanodine receptor	Ca^{2+} channel on sarcoplasmic reticulum	agonist of ryanodine receptor	(66–73)

Tab.2.Toxicity data about caffeine.

Description	Value	References
Manifestation of poisoning	129 $\mu\text{mol/l}$ (plasma level)	(81,82)
Peak plasma concentration after taking 100 mg of caffeine	10.3 $\mu\text{mol/l}$ (men) / 18.5 $\mu\text{mol/l}$ (women)	(25)
Rat (LD_{50})	155 mg/kg	(86)
Dog (LD_{50})	140 mg/	(87)
Water flea <i>Ceriodaphniadubia</i> (LC_{50})	60 mg/l	(88)
Fathead minnow fish <i>Pimephalespromelas</i> (LC_{50})	100 mg/l	(88)
Nematoceran flies <i>Chironomusdilitus</i> (LC_{50})	1230 mg/l	(88)

LD_{50} – median lethal dose; LC_{50} – median lethal concentration

or even excluded the hypothesis (78). Contrary, some anti-cancer effects of caffeine are mentioned in the current literature(79,80). The whole issue deserves a deeper insight and perhaps it will be target of an extensive clinical search.

Though it can appear that only minor effect of caffeine is mediated through adenosine receptors when considered the aforementioned works, the contrary is true. Affinity of caffeine to the other targets is typically lower than the affinity to adenosine receptors, so the biological role of the other targets should be considered carefully and needs further effort to be understood how significant it is in real conditions. The signaling pathways mentioned in the text are summarized in the Table 1.

Caffeine toxicity

Toxicity of caffeine is low and there are no or minimal adverse effects when caffeine is taken by a beverage or food. It is assumed that manifestation of caffeine toxicity appears when its plasmatic concentration reaches 129 $\mu\text{mol/l}$ (i.e. 25 mg/kg in mass scale) as demonstrated on a case report (81,82). Overdosing by caffeine is not a common phenomenon and it can occur due to wrong application of food supplements or drugs containing caffeine. Abusing of caffeine via food or beverages is not known in the current medicine and stimulating pills or substances for fitness are the more treating forms of caffeine in this point of view. Banerjee and co-workers have analyzed the cases of fatal caffeine intoxication and stated that the average postmortem concentration of caffeine was 140 mg/l (83). The intoxicated people died due to cardiac arrhythmias, seizures can also occur in the overdosed. Abusing of caffeine can be clearly demonstrated on a case report described by Jabbar and Hanly(84). They reported a case of a 39 year old man overdosed by 12 g of pure caffeine. As proved by autopsy, the man had blood caffeine level 350 mg/l.

Safety of caffeine containing beverages and food can be inferred from the following example. Yubero-Lahoz and co-workers tested the concentration of caffeine in plasma of men and women after drinking a cup of coffee with 100 mg of caffeine (25). The male subjects exerted caffeine peak concentration in plasma 2.0 mg/l (10.3 $\mu\text{mol/l}$) while the female subjects 3.6 mg/l (18.5 $\mu\text{mol/l}$). The amount of caffeine in beverages can differ from each other because of the technological and individual reasons. In literature, concentration of caffeine 120.5 mg/l for green tea, 149.5 mg/l for black tea, 267.5 mg/l for coffee, 94.1 mg/l for Coca Cola and 55.5 mg/l for Pepsi can be found (85). When considered the text above, it is clear that the current beverages have too low concen-

tration of caffeine to make serious overdosing. A man should take tens of cups of coffee at a blow to reach plasmatic concentration of caffeine so high to threaten his life.

Caffeine seems to be harmless compound since the median lethal doses (LD_{50}) for caffeine are high. In examples, LD_{50} is 155 mg/kg for rats (86) and 140 mg/kg for German shepherd dogs (87). Quite a high range of median lethal concentration (LC_{50}) is reported for water organisms but the water organisms exert also considerable tolerance to caffeine. Water flea (*Ceriodaphniadubia*) exerted LC_{50} 60 mg/l, fathead minnow fish (*Pimephalespromelas*) 100 mg/l, and nematoceran flies *Chironomusdilitus* 1230 mg/l in one experiment(88). On the other hand, people should be aware of some adverse effects that precede toxicity manifestation (see later). Toxicological data for caffeine are summarized in the Table 2.

Compared to adults, children are more sensitive to caffeine and overdosing can arise much early and unforeseen (89). Special caution to caffeine should be given to pregnant women and fetus. In an experiment on zebrafish embryos, caffeine significantly modulated their moves during development and the embryos exerted abnormality in skeletal muscles formation (90). Angiogenesis is altered by caffeine in zebrafish model as well (91). Retardation of intrauterine growth and impaired fetal length growth were indicated for Wistar rats receiving caffeine 120 mg/kg in 11–20 gestational days (92). Caffeine can further worsen toxicity to fetus of some other compounds. This fact was approved by e.g. Nikoui and co-workers for clomipramine (93). In humans, fecundability is reduced in women taking more than 300 mg of caffeine per day (94). The other adverse effect including a decline of fetal development is also expected in humans (95). On the other hand, doses of caffeine under approximately 200 mg a day can be considered harmless in pregnancy. Jahanfar and Jaafar demonstrated that a dose of caffeine 182 mg per a day had no effect on birthweight or length of gestation (96).

Some controversies can be found for caffeine and infertility. Some works are concluded by a statement that caffeine has no influence on woman fertility (97), but the conclusions are not identical in other sources (98). Moreover, caffeine is suspected to be implicated in male infertility (99). In a small pilot study, avoiding of risk factors such as alcohol drinking, smoking and coffee intake, was proved to have a positive role on fertility, while abusing the aforementioned leads to fertility impairment(100). When considering studies, it is not easy to distinguish what is the cause and what the consequence. The role of caffeine in infertility should be evaluated carefully. Molecular mechanism how caffeine could initiate infertility is not clear as well. Moreover, caffeine addi-

Tab.3. Basic data about medications containing caffeine.

Effective substances	Purpose	Example of trade names or patents
Caffeine	suppression of sleep and fatigue	Enerjets, No Doz, Vivarin
Acetylsalicylic acid, caffeine	analgesic, antipyretic and stimulant drug for ameliorating e.g. influenza etc.	Anacin, Antidol, Atasol, Astone Cap, Calmine, Pain Aid
Acetylsalicylic acid, caffeine, codeine		AC&C, Painex
Paracetamol (acetaminophen), caffeine, codeine		Atasol, Acet, Corytab, Cotabs, NovoGestic
acetylsalicylic acid, butabital, caffeine		Trianal, Ratio-Tecnal
Paracetamol, butabital, caffeine		Esgic-Plus, Orbivan
Ergotamine, caffeine		Wigraine
Nicotine, tryptophan, phenylalanine, tyrosine and caffeine	pain relieve in migraines	patent CA2826019 A1 (109)
Lecithin organogel, an ethylene oxide-propylene oxide ethylene oxide triblock copolymer, caffeine, retinoid,	cellulite	patent US 2013/0210840 A1 (113)
yacon (<i>Smallanthus sonchifolius</i>) with caffeine and some vitamins (C, H, B6, D3) and admixtures	weight loss	patent CA2747904 A1 (114)

tive to semen during in vitro fertilization improves probability of pregnancy (101). This conclusion is in a little contradiction to the clinical tests. More work on the issue should be done prior to make the final conclusion.

The current use of caffeine in pharmacology

Caffeine is known as a cognitive enhancer. It has no plausible effect on memory or ability to learn except of suppression of fatigue; however, it improves hedonic tone and reduces anxiety when given in a low dose (102). When dose of caffeine is increased, tense arousal, anxiety, nervousness and jitteriness can be expected. Even caffeine neurosis can occur in rare cases of caffeinism (103). It is widely discussed if r caffeine can modulate progression of cognitive decline in patients suffering from neurodegenerative disorders (104). Lower incidence of Alzheimer disease was found in humans who regularly take coffee when compared to ones, who have not taken coffee during their lives (105,106). Etiology of Alzheimer disease remains unrevealed hence mechanism of caffeine implication in the disease can be only speculated; on the other hand, beneficial effect of caffeine is considered to be plausibly proved (107). Considering the aforementioned anti-inflammatory effect of caffeine and the fact that neuro-inflammation is considered as either reason or one of Alzheimer disease mechanism, caffeine can take its effect just this way. Surprisingly, no therapy based on caffeine was established for Alzheimer disease. Similar conclusion can be made for Parkinson disease, where caffeine beneficial effect was proved in some studies, but the mechanism remains a mystery (108).

Caffeine is utilized as a drug additive in some medications or as a major substance in drugs for suppression of sleep and fatigue. Pure caffeine is sold in form of tablets with 200 mg of caffeine or lozenge with 75 mg of caffeine. Brand names Enerjets, No Doz and Vivarin can be mentioned as examples of the marketed products. Caffeine is also added to medications for suppression of influenza and similar viral infections manifestation. The medications contain caffeine as a stimulant and an antipyretic and analgesic substance such as acetylsalicylic acid (e.g. Anacin, Antidol, Atasol, Astone Cap, Calmine, Pain Aid) or paracetamol. The an-

algetic effect can be further graduated by addition of an opiate, which can result in significant antitussive properties. Codeine in combination with caffeine and either paracetamol (medications Atasol, Acet, Corytab, Cotabs, NovoGestic) or acetylsalicylic acid (AC&C, Painex) is known. Similar indication has medicaments where butabital is used instead of codeine. Caffeine is added to tablets for pain relieve during migraines. For the migraines, commercial medication Wigraine contains 1 mg of ergotamine tartrate and 100 mg of caffeine per one tablet. An invented medicament containing nicotine, tryptophan, phenylalanine, tyrosine and caffeine would be an improvement to the current drugs for migraines (109). Caffeine can provide a relieve in post-lumbar puncture headache appearing after lumbar puncture or epidural anesthesia. It is an iatrogenic problem complicating a recovery of patients. Caffeine can be applied and it is very effective in both prophylaxis and treatment of post-lumbar puncture headache (110–112). Compositions of medicaments containing caffeine and chosen brand names are written in the Table 3.

Besides the currently used drugs, caffeine is intended to be added to new preparations for several reasons. Grasela and co-workers invented a preparation for treating cellulite composed of lecithin organogel, ethylene oxide-propylene oxide ethylene oxide triblock copolymer, caffeine, retinoid, and optionally some vitamins (113). Extract from plant yacon (*Smallanthus sonchifolius*) with caffeine and some vitamins (C, H, B6, D3) and/or other effective substances from disparate plants (e.g. *Lycium barbarum*, *Malpighia glabra*, *Vaccinium corymbosum*, *Punicagranatum*) was invented as a medicament for weight loss (114).

Expected application of caffeine in pharmacology

Caffeine has a significant use in the medications described in the previous chapter. However, the current use is dominantly based on the addition of caffeine as a supplementary substance. On the other hand, the current status can change because of the recent findings devoted to a protective effect of caffeine in Alzheimer disease associated pathologies including deposition of amyloid precursor 42 (105). Intake of 3–5 cups of coffee per a day is significantly associated with a lower incidence of Alzheimer disease

Tab.4. Caffeine effect on diseases where no pharmacologically application of caffeine is known.

Disease	Effect of caffeine	Manifestation of caffeine	Dose	Reference
Alzheimer disease	positive	later onset and slower progression of the disease	3 – 5 cups of coffee per a day	(115)
Parkinson disease	positive	later onset and slower progression of the disease	3 cups of coffee per a day	(124)
Huntington's disease	negative	early onset of the disease	> 190 mg per a day	(130,131)

(115). Unfortunately, no therapy or prophylaxis based on caffeine application has been established. On the other hand, coffee as a food supplement is accessible and some preparations are invented to be added to food in order to ameliorate the neurodegenerations. As an example, Chu and co-workers invented the mixture containing caffeine and polyphenolic antioxidants that would be used for the purpose useful for facilitating neuroprotection, inhibition of cyclooxygenase 2 or stimulating glucose uptake (116). The authors postulated that crude caffeine containing other biologically active substances exert beneficial effect due to the presence of the non-caffeine components. They proved their postulation on cell lines where cells were plausibly more resistant to an oxidative insult and/or other inflammatory stimuli.

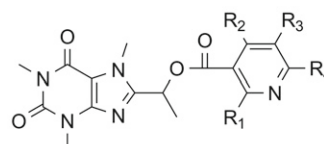
Caffeine is easily accessible in a pure form and there are available patented protocols for caffeine purification from crude mass (117–120). Besides standard routes, caffeine can be delivered by an electronic cigarette (121) or by microparticles for sustained release (122) hence the application is not needed to be limited to pills and solutions. Other mixtures were prepared in order to reduce a side effect of caffeine. Crain and co-workers invented the mixture of caffeine with compounds selectively blocking or inhibiting opioid receptor signaling naltrexone, naloxone, diprenorphine, nalmefene, norbinaltorphimine, neuraminidase inhibitors methylsulfonylmethane, magnesium sulfate, sodium sulfate, chondroitin sulfate, n-acetyl-cysteine, zanamivir, laninamivir, peramivir, oseltamivir and 5,7,4',-trihydroxy-8-methoxyflavone (123). On the other hand, it is questionable if such mixture will keep the ability to reduce manifestation of the mentioned neurodegenerations. Test on the issue should be done prior to make a conclusion.

Similarly to Alzheimer disease, caffeine is able to significantly ameliorate a progression of Parkinson disease. Currently, 3 cups of coffee a day are considered as the maximal protective source of caffeine for preventing from Parkinson disease (124). Even Machado-Joseph Disease progression will be improved by caffeine as well (125). Similarly to Alzheimer disease, the etiology of Parkinson disease is not known and it is hard to propose an effective therapy when it is not clear where to aim the new drugs. Why caffeine is effective in the prevention of Parkinson disease is not known. Maybe anti-neuroinflammation combined with a reduction of neuron's oxidative damage is behind the protective effect (126). Molecular mechanism of such effect is again hardly to be tracked and some pathways can be only hypothesized (32). Nevertheless, caffeine is considered as a perspective compound able to ameliorate neurodegenerative disorders and would serve as the lead structure in pharmacology research on the issue (127). Besides the use of caffeine for therapeutic purposes, it was considered as a reagent in a test for diagnosis of Alzheimer disease (128). The test; however, has not become widely used in laboratory praxis so its validity cannot be confirmed.

Owing to neurodegenerative disorders, caffeine does not have a beneficial role only. It is known that caffeine is negatively implicated in the Huntington's disease. Comparing to the aforementioned neurodegenerative disorders, Huntington's disease is genetically determined and typically starts much earlier than Alzheimer or Parkinson disease (129). Caffeine causes earlier onset of Huntington's disease and should be avoided in the individuals with prognosis to the disease (130,131). There are probably more mechanisms of an early onset and progression of Huntington's disease, and they remain misunderstood (132,133). However, molecular mechanism of an early onset of Huntington's disease should be further researched prior to make a simple conclusion. Summarization of caffeine implication in the mentioned neurodegenerations is given in the Table 4.

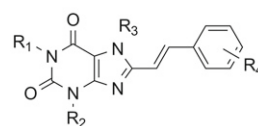
Derivatives with caffeine moiety and their use

Attempts to prepare modified caffeine were made during a long time. Invented 8-beta-dimethylaminoethoxycaffeine, 8-beta-dimethyl-aminoethoxycaffeine, 8-beta-diethylaminoethoxycaffeine, 8-beta-diethyl-aminoethoxycaffeine, 8-beta-diethyl-aminoethoxy-caffeine and protocols for their synthesis can be mentioned as an early effort to use caffeine (134). However, the simple derivatives of caffeine did not overcome caffeine in the both biological effects and costs and the compounds were not introduced to market as drugs or food supplements. Compounds based on caffeine with broncholytic activity (Fig. 3) were also invented and preclinically tested (135). Caffeine, as well as the other adenosine antagonists, can be used for protection against cardiac ischemia (136). The fact was utilized by Liang and Jacobs who invented caffeine derivatives (Fig. 4) and made basic tests for their efficacy (137). The invented 8-(3-chlorostyryl) caffeine derivatives were used as A_{2A} adenosine receptor antagonists and the authors depicted the beneficial effect on cell lines. These findings can appear as ridiculous



where R₁ - R₄:
hydrogen, chlorine,
bromine, an alkyl or
an alkoxy group.

Fig. 3. Basic structure of invented caffeine derivatives with broncholytic activity (135).



where:
R₁, R₂ - methyl, ethyl, propyl, allyl
R₃ - H, methyl, alkyl, with 2 - 8 carbons
R₄ - H, MeO, NH₂, NO₂, F, Cl, etc.

Fig.4. Caffeine derivatives for cardiac ischemia treating (137).

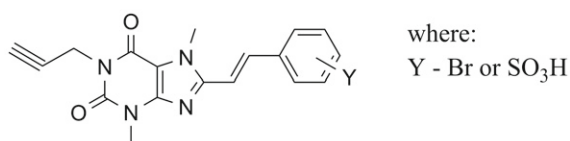


Fig. 5. Selected caffeine derivatives for hepatic fibrosis, cirrhosis and fatty liver formation treating (141).

because tachycardia resulting from caffeine effect will worsen the ischemia. Caffeine as well as the other compounds antagonizing or agonizing A_{2A} adenosine receptor have a potential to modulate striatopallidal pathway that represents a link between the cardiovascular system and the brain parenchyma (138–140). Beneficial effect of caffeine and caffeine derived compounds in cardiac ischemia despite of risk of tachycardia can be explained just by the striatopallidal pathway. A group of caffeine derived compounds was also prepared by Cronstein et al (Fig. 5) and the authors proved efficiency of their compounds on in vitro tests (141). The other caffeine containing moiety compounds were prepared in order to use their antagonism on adenosine receptors and other targets structures as well. In an example, Ivatchenko and co-workers invented 2,6-dioxo-2,3,6,7-tetrahydro-1H-purine-8-yl derived compounds and claimed their potency to be used for disparate purposes in pharmacology (142). Quite similar compounds were prepared by Palle and co-workers (143). The authors claimed that the prepared compounds deserved attention for future research and would be suitable in therapy of asthma, chronic obstructive pulmonary disorder, angiogenesis, pulmonary fibrosis, emphysema, allergic diseases, inflammation, reperfusion injury, myocardial ischemia, atherosclerosis, hypertension, congestive heart failure, retinopathy, diabetes mellitus, obesity, inflammatory gastrointestinal tract disorders, and/or autoimmune diseases. The expected use is however, not confirmed by an extensive test so the compounds should be further researched. Besides the aforementioned, caffeine derivatives were also prepared for e.g. extra-pyramidal syndrome (144) and therapy of Parkinson's disease (145). The all mentioned patents would be promising but more work to characterize prepared compounds should be done.

Modified caffeine moiety can be found in cafedrine and theodrenaline (Fig. 6). The compounds are available as e.g. drug Akkrinor for treatment of acute hypotension (146,147). The effect of Akkrinor is manifested by an increase of cardiac output and venous return. No comparable drugs are available (148). Effect of cafedrine and theodrenaline is mediated via alpha 1 adrenaline receptor, adenosine receptors do not have a role in the effect (149).

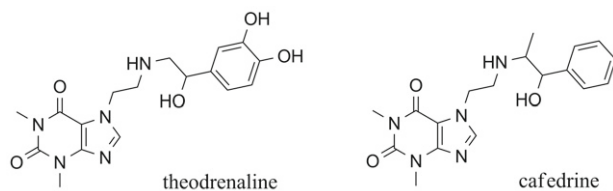


Fig. 6. Structure of cafedrine and theodrenaline.

Conclusion

Caffeine is a simple compound with a significant effect on the body. Though the major pathways of caffeine are revealed, a lot of mysteries about caffeine remain. Especially the links between caffeine and neuroinflammation as well as neurodegenerative disorders are proved, but not understood in their principles. Nevertheless, promising mixtures of caffeine with other effective substances and/or caffeine derivatives were prepared and published or invented. Practical impact of the findings is expected and the role of caffeine in the pharmacology probably will probably increase in the future.

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