PERSPECTIVES

The perspective of caffeine and caffeine derived compounds in therapy

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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).

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 leafs 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 leafs (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
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. Biological synthesis, metabolism and pharmacokinetics of caffeine

![Fig. 1. Synthesis of caffeine in the plants.](image1)

![Fig. 2. Caffeine demethylation to paraxanthine.](image2)
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 A1, A2A, A2B, and A3 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). The mental sedation because of receptor A2A and bradycardia via receptors A1 as well as A2B are typical manifestations of agonism and the oppose effect is evoked just by caffeine (37,38). The A1 isotype is also involved in the regulation of neutrophils and its degranulation (39,40). From the mentioned receptors, the isotype A2B is dominantly located in central nervous system, especially in the extrastriatal 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 A2A 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 A2B receptors (46). In the bronchus, caffeine can suppress bronchospasm and even significantly ameliorate bronchoconstriction just by antagonizing the A2B (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, dopamine 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 scarred 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 hasesmall 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 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 results 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 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 Ca2+ (66–70). Caffeine is a full agonist on the ryanodine receptors and it forces Ca2+ transient (71–73) also is used as controlsin experiments where Ca2+ 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.

<table>
<thead>
<tr>
<th>Target structure</th>
<th>Role of the target structure</th>
<th>Effect of caffeine</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetylcholinesterase</td>
<td>it splits neurotransmitter acetylcholine</td>
<td>non-competitive inhibitor of acetylcholinesterase</td>
<td>(32,59–62)</td>
</tr>
<tr>
<td>Adenosine receptors</td>
<td>G protein coupled receptor mostly implicated in sedation (bradycardia, suppression of mental excitation etc.)</td>
<td>competitive antagonist on adenosine receptors</td>
<td>(37–44,47,48)</td>
</tr>
<tr>
<td>Monoamine oxidase</td>
<td>oxidizes epinephrine, norepinephrine, serotonin, and dopamine</td>
<td>reversible monoamine oxidase</td>
<td>(57,58).</td>
</tr>
<tr>
<td>Phosphodiesterase</td>
<td>the enzyme hydrolyzes secondary intracellular messengers cAMP and cGMP</td>
<td>reversible inhibitor of phosphodiesterase</td>
<td>(64,65)</td>
</tr>
<tr>
<td>Poly(ADP-ribose)polymerase</td>
<td>DNA repair, apoptosis</td>
<td>reversible inhibitor of poly(ADP-ribose)polymerase</td>
<td>(75–77)</td>
</tr>
<tr>
<td>Ryanodine receptor</td>
<td>Ca2+ channel on sarcoplasmic reticulum</td>
<td>agonist of ryanodine receptor</td>
<td>(66–73)</td>
</tr>
</tbody>
</table>
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 μmol/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 μmol/l) while the female subjects 3.6 mg/l (18.5 μmol/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 concentration 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 (LD₅₀) for caffeine are high. In examples, LD₅₀ is 155 mg/kg for rats (86) and 140 mg/kg for German shepherd dogs (87). Quite a high range of median lethal concentration (LC₅₀) is reported for water organisms but the water organisms exert also considerable tolerance to caffeine. Water flea (Ceriodaphnia dubia) exerted LC₅₀ 60 mg/l, fathead minnow fish (Pimephales promelas) 100 mg/l, and nematoceran flies (Chironomus dilutus) 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/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-

<table>
<thead>
<tr>
<th>Description</th>
<th>Value</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manifestation of poisoning</td>
<td>129 μmol/l (plasma level)</td>
<td>(81, 82)</td>
</tr>
<tr>
<td>Peak plasma concentration after taking 100 mg of caffeine</td>
<td>10.3 μmol/l (men) / 18.5 μmol/l (women)</td>
<td>(25)</td>
</tr>
<tr>
<td>Rat (LD₅₀)</td>
<td>155 mg/kg</td>
<td>(86)</td>
</tr>
<tr>
<td>Dog (LD₅₀)</td>
<td>140 mg/</td>
<td>(87)</td>
</tr>
<tr>
<td>Water flea Ceriodaphnia dubia (LC₅₀)</td>
<td>60 mg/l</td>
<td>(88)</td>
</tr>
<tr>
<td>Fathead minnow fish Pimephales promelas (LC₅₀)</td>
<td>100 mg/l</td>
<td>(88)</td>
</tr>
<tr>
<td>Nematoceran flies Chironomus dilutus (LC₅₀)</td>
<td>1230 mg/l</td>
<td>(88)</td>
</tr>
</tbody>
</table>

LD₅₀ – median lethal dose; LC₅₀ – median lethal concentration.
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 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 toones, 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, the current status can change because of the recent findings devoted to a protective effect of caffeine in Alzheimer disease (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 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 are written in the Table 3. However, the current use is dominantly based on the addiction of caffeine as a supplementary substance. On the other hand, 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 some vitamins (C, H, B6, D3) and admixtures. Pure caffeine is sold in form of tablets with 200 mg of caffeine or lozenge with 75 mg of caffeine. Brand names are written in the Table 3. The inventors of this preparation is considered to be Pliva (113). Extract from plant yacon (Smallanthus sonchifolius) with caffeine and some vitamins (C, H, B6, D3) and admixtures was invented as a medicament for weight loss.

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 addiction 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. Caffeine has a significant use in the medications described in the previous chapter. However, the current use is dominantly based on the addiction 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.
Tab.4. Caffeine effect on diseases where no pharmacologically application of caffeine is known.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Effect of caffeine</th>
<th>Manifestation of caffeine</th>
<th>Dose</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alzheimer disease</td>
<td>positive</td>
<td>later onset and slower progression of the disease</td>
<td>3 – 5 cups of coffee per a day</td>
<td>(115)</td>
</tr>
<tr>
<td>Parkinson disease</td>
<td>positive</td>
<td></td>
<td>3 cups of coffee per a day</td>
<td>(124)</td>
</tr>
<tr>
<td>Huntington’s disease</td>
<td>negative</td>
<td>early onset of the disease</td>
<td>&gt; 190 mg per a day</td>
<td>(130,131)</td>
</tr>
</tbody>
</table>

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 methylsulfonyl-methane, magnesium sulfate, sodium sulfate, chondroitin sulfate, n-acetyl-cycteine, 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. They proved their postulation on cell lines where 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).

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-dimethylaminoothoxycaffeine, 8-beta-dimethyl-aminoothoxycaraffeine, 8-beta-diyethylaminoothoxycaffeine, 8-beta-diethyl-aminoothoxycaffeine, 8-beta-diethyl-aminoothoxycaffeine 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 A2A adenosine receptor antagonists and the authors depicted the beneficial effect on cell lines. These findings can appear as ridiculous.

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

Fig. 4. Caffeine derivatives for cardiac ischemia treating (137).
because tachycardia resulting from caffeine effect will worsen the ischemia. Caffeine as well as the other compounds antagonizing or agonizing A2A 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-1-urine containing moiety compounds were prepared in order to use suitable in therapy of asthma, chronic obstructive pulmonary diseases, in diabetes mellitus, obesity, in atherosclerosis, hypertension, congestive heart failure, retinopathy, 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 patients 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 Akrinor for treatment of acute hypotension (146,147). The effect of Akrinor 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. 5. Selected caffeine derivatives for hepatic fibrosis, cirrhosis and fatty liver formation treating (141).

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.

References


68. Gaburjakova J, Gaburjakova M. Coupled gating modifies the regulation of cardiac ryanoide receptors by luminal cal(2+). Biochim Biophys Acta 2014; 1838 (3): 867–873.


106. Vila-Luna S, Cabrera-Isidoro S, Vila-Luna L et al. Chronic caffeine consumption prevents cognitive decline from young to middle age in rats, and is associated with increased length, branching, and spine density of basal dendrites in cal1 hippocampal neurons Neuroscience 2012; 202: 384–395.


137. Liang BT, Jacobson KA. Methods for protecting against cardiac ischemia by administering adenosine a2a receptor antagonists; us5859019. 1999.


141. Cronstein BN, Chan E. Adenosine a2a receptor antagonists for treating and preventing hepatic fibrosis, cirrhosis and fatty liver; us 6535545 b2. 2003.

142. Ivachchenko AV, Mitkin OD, Kadieva MG, M. OL. Substituted phenoxycetic acids and esters and amides thereof, comprising a, 6-di-oxo-2, 3, 6, 7-tetrahydro-1H-purine-8-yl fragment and constituting a2a adenosine receptor antagonists, and the use thereof; wo 2013058681a3. 2012.


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