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A Short Review on the Effect of Functional Group in Methylxanthine (Caffeine) Class of Drugs

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Abstract

In general, drugs play a vital role in our day to day life to heal several diseases. However, higher doses of drug which initiates the side effect and leads to chronic disease. Among the drugs, this occupies a unique position because of its own functional properties. The methylxanthine derivatives are also largely consumed as a psychoactive alkaloid drug that includes Caffeine ($C_8H_{10}N_4O_2$), Theophylline ($C_7H_8N_4O_2$), Paraxanthine ($C_7H_8N_4O_2$), Pentoxifylline ($C_{13}H_{18}N_4O_3$), Theobromine ($C_7H_8N_4O_2$), Aminophylline ($C_{16}H_{24}N_{10}O_4$), and IBMX-3-Isobutyl-1-methylxanthine ($C_{10}H_{14}N_4O_2$) and it has been stimulating particular parts of the nervous system in the human body. Especially this drug is consumed in the name of coffee more than 80% of people all over the world without knowingly or unknowingly the impact of caffeine. This paper deals with the effect of functional groups of methylxanthine having $-NH_2$, $-C=O_2$, $-CONH_2$.

Keywords: Caffeine; Xanthine; Derivatives; Receptors; Central nervous system; Effects of functional groups

Abbreviations: NASA: National Aeronautics and Space Administration; DNA: Deoxyribonucleic acid; RNA: Ribonucleic Acid; UV: Ultra Violet; CNS: Central Nervous System; cAMP: Cyclic Adenosine Monophosphate; ^{0}C: Degrees Celsius; LD_{50}: Lethal Dose 50%; Na^+/K^+ ATPase: Sodium ion/Potassium Ion Adenosinetriphosphatase; COPD: Chronic Obstructive Pulmonary Disease; $-CH_3$: Methyl Group; -C=O: Carbonyl Groups; -C=C: Alkene Group; -C=N: Imine Group; g/mol: Gram Per Mole; IUPAC: International Union of Pure and Applied Chemistry; GMP: Cyclic Guanosine Monophosphate; PDE: Phosphodiesterase; IBMX: 3-isobutyl-1-methylxanthine; GABA: Gamma-Aminobutyric Acid; A_1, A_2A and A_2B: Adenosine Receptors; XO: Xanthine Oxidase.

Introduction

Generally, heterocyclic compounds are more essential for a human life due its properties. In this category methylxanthine drug that has some applications for respiratory issues, asthma and chronic obstruction pulmonary disease. Other than these applications of methylxanthine there are compounds that include caffeine, theophylline, paraxanthine, pentoxifylline theobromine, aminophylline and IBMX-3-Isobutyl-1-methylxanthine. These compounds are benzo-fused heterocyclic compounds that are used as a stimulant for central nervous system [1].

The aromatic heterocyclic compound can have many nitrogen atoms but it has only one sulfur or oxygen in a ring instead of one carbon atom, it stimulates the heart beat-rate, cardiac arrhythmias and force of contraction at higher doses. These are also purine base compounds that are available in plants like tea, coffee and animals that consume indirectly by means food or drinks. Xanthine related compounds are also present in DNA and RNA as adenine and guanine. A study by NASA on 11th August 2011, stated that meteorite which contains xanthine and other related organic compounds including DNA, RNA and also found in space also.

Among the above compounds, caffeine is a peculiar compound which is more abundant in the earth and it is a natural stimulant in tea, coffee and other non-alcoholic beverages. They have remarkable resistance against sleepiness by inducing adenosine. Plants like guarana, yerba mate, kola, guayusa and holly contains caffeine [2]. The methylxanthine compounds can be detected through UV and Fourier transform infrared spectroscopic techniques (Figure 1).

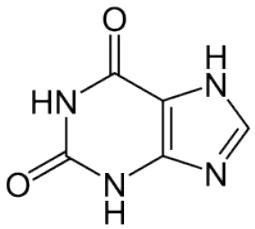

Figure 1: Methylxanthine.

Caffeine

Caffeine is a simple purine base compound and it is a moderately soluble about 2 g/100 mL in water at room temperature. It tastes bitter, white, odorless substance with melting point 235-238^{0}C. Coffee and tea have owed stimulant properties to caffeine, a simple trimethyl purine derivative. It has an imidazole ring fused to a pyrimidine ring and it is aromatic according to huckle's rule despite of the two carbonyl groups.

In 1819, a German chemist named Friedlieb Ferdinand Runge isolated comparatively pure caffeine for the first time; he also called it as "Kaffebase" that exists in coffee [2]. According to Runge, he did this under the instructions of Johann Wolfgang von Goethe who was non-professional botanist.

In 1821, caffeine was isolated both by the French chemist Pierre Jean Robiquet and by further another pair of French chemists, Pierre-Joseph Pelletier and Joseph Bienaimé Caventou, according to a journal article by Jöns Jacob Berzelius. Further experiments were

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done according to Berzelius. He stated that the French chemists had made their discoveries independently without any prior knowledge of Runge's or each other's work [3]. But Berzelius thereafter acknowledged Runge's priority in the extraction and isolation of caffeine.

Robiquet was one among the first to isolate and outlined the properties of pure caffeine whereas Pelletier was the first to execute an elemental analysis [4].

In 1827, M Oudry discovered "théine" from tea yet it was after proved by Mulderand Carl Jobst that theine compound was authentically caffeine that was present.

In 1895, German chemist Hermann Emil Fischer first synthesized caffeine from its chemical components and that was a total synthesis. Then two years later, he as well derived the structural formula of the compound and this part of his work, Fischer was awarded the Nobel Prize in 1902.

Pharmacodynamics of caffeine

In the absence of caffeine, when a person is not at sleep and vigilant, some quantity of adenosine is present in central nervous system (neurons). If the body is continuously at wakeful state over time it gets occupied in the neuronal synapse in order for binding and activating adenosine receptors that are already on certain central nervous system neurons that are activated, these receptors induce a cellular response that eventually increases drowsiness. When caffeine is taken, it antagonizes adenosine receptors. Similarly, caffeine prevents adenosine from activating the receptor by inhibiting the action on the receptor where adenosine binds to it. Finally, caffeine temporarily prevents or reduces drowsiness, and thus enables and restores alertness [5].

Pharmacokinetics of caffeine

When caffeine is consumed through regular intake or drinking, the human body gets caffeinated through the blood stream. Caffeine gets circulated and eventually approaches the liver, where the reaction undergoes in the liver to make it into smaller components, and these smaller components are called metabolites. There are three catabolism occur to produce three different metabolites. 84% of caffeine is broken down into smaller components to form paraxanthine that affects the levels of fat in the blood and helps to keep the body sleepless, 12% of caffeine is broken down into theobromine that causes the blood vessels to enlarge and promotes the outcome of urine and 4% of caffeine is broken down into theophylline that causes the airways to get widen and forging it easier to breathe. Ultimately, caffeine has ability to cross the blood-brain barrier that means it can transfer from the blood stream into the brain and it works as a stimulant. Precisely in the brain, caffeine obstructs the effects of a neurotransmitter that is adenosine, a molecule that encourages drowsiness. It also temporarily increases the production of dopamine that functions primarily as a local chemical messenger (Figure 2).

Functional groups in caffeine

In organic chemistry, there are several functional groups having specific characteristic properties. Familiar functional groups are amine, alcohol, aldehyde, ketone, ester, ether, amide, and carboxylic acid. But all functional groups are not present in xanthine derivatives (Figure 3).

In caffeine, C=O following to a Nitrogen is an amide group and there are two amide groups in the ring. So it contains two amine and two amide functional groups that exhibit special properties. The caffeine molecule also contains methyl groups (-CH_3), carbonyl groups (-C=O), an alkene group (-C=C) and also an imine group (-C=N).

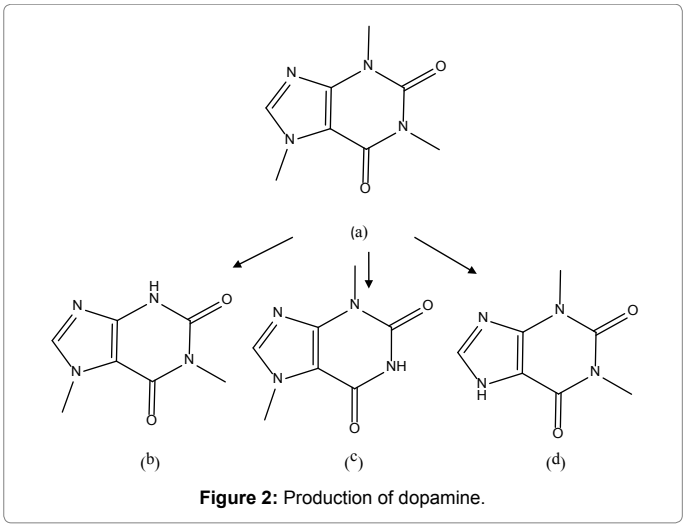

Figure 2: Production of dopamine.

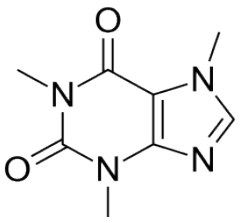

Figure 3: Xanthine.

Theobromine

Theobromine or 3,7-dimethylxanthine, it is principle alkaloid in *Theobroma cacao* (cacao bean) and it is present in other plants also. It is a xanthine alkaloid that is widely used as a bronchodilator and vasodilator. Theobromine has a weaker diuretic activity than theophylline and has less powerful stimulant of smooth muscle. It has no practically stimulant effect on the central nervous system.

It is a bitter alkaloid of the methylxanthine derivative that too includes the similar compounds of theophylline and caffeine. This compound does not contain bromine. But theobromine is derived from Theobroma, the genre of the cacao tree that is composed of the Greek roots theo (God) and broma (food) means "food of the gods".

It is the primary alkaloid found in cocoa and chocolate, and is one of the sources for chocolate's mood-elevating effects. The quantity of theobromine found in chocolate is small enough that chocolate can be safely consumed by humans in large quantities, however animals that metabolize theobromine more slowly, for some extend it is poisonous to cats and dogs but it is less toxic to rats, mice, and humans, who all have an LD_{50} of about 1,000 mg/kg.

Theobromine is different from caffeine. Theobromine has very different effects on the human body from caffeine; it is a mild, lasting stimulant with a mood improving effect, whereas caffeine is stronger than theobromine, it has immediate effect and increases stress.

In medicine field it is used as a diuretic, vasodilator, and myocardial stimulant. There is a possible association between prostate cancer and theobromine. It is not currently used as a drug (Figure 4) [6].

Functional groups in theobromine

Functional groups those are present in theobromine as comparing

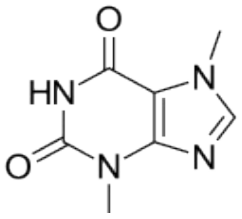

Figure 4: Theobromine.

with the caffeine that has similar structure as this compound. So it contains two amine and two amide groups as caffeine but the number of methyl groups that are there in caffeine is three but in theobromine, the number of methyl group is two and one methyl group is substituted with hydrogen atom. It also contains an alkene group (-C=C) and also has an imine group (-C=N) as caffeine.

Paraxanthine

1,7-dimethylxanthine or Paraxanthine is a dimethyl derivative of xanthine, and it has same structurally relationship as caffeine. Similarly caffeine and paraxanthine is a psychoactive central nervous system (CNS) stimulant. It possesses a potency roughly same to that of caffeine and is likely involved in the mediation of the effects of caffeine itself.

Paraxanthine is being the main metabolite in human body [7]. It is not build by plants and however it is only detected in nature as a metabolite of caffeine and theobromine in animals. After consumption, approximately 84% of caffeine is demethylated at the 3-position to yield paraxanthine, making it as a chief metabolite of caffeine in the body [8].

Paraxanthine is a competitive nonselective phosphodiesterase inhibitor which raises intracellular cAMP [1]. Paraxanthine sometime responsible for the lipolytic properties of caffeine, and presence of this compound in the blood can leads to increase in serum free fatty acid concentration [9]. Paraxanthine differ from caffeine as it reacts as enzymatic effectors of Na^+/K^+ ATPase. Finally, it is responsible for increased transfer of potassium ions into skeletal muscle tissue and it can increase the calcium ion concentration in muscle [10,11].

It is believed to exhibit a lesser toxicity than caffeine though blood levels commensurate with average consumption appear to be fairly harmless, high blood concentrations of paraxanthine have been linked to the loss of pregnancy in pregnant women (Figure 5) [12].

Functional groups in paraxanthine

The functional group that are present in paraxanthine are present in this compound is identical as theobromine that contains a two amide groups, two methyl groups and the position of NH- group that is present in paraxanthine is at para-position. It also contains an alkene group - C=C and also an imine group -C=N. The total number of carbon, nitrogen, oxygen and hydrogen numbers are same as in theobromine.

Theophylline

1,3-dimethylxanthine or Theophylline is a methylxanthine derivative from tea. It has a smooth muscle relaxant, diuretic, bronchial dilation, cardiac and central nervous system stimulant behaviors. Automatically it acts as a phosphodiesterase inhibitor, adenosine receptor blocker, and histone deacetylase activator. Theophylline is marketed under several brands and it is indicated mainly for asthma, bronchospasm, and COPD (Figure 6).

Functional groups in theophylline

Functional groups that are incorporated in this compound are two amide groups and groups that are present other than functional properties are two methyl groups, an imine and alkene carbon atoms. There is no substitution of hydrogen instead of methyl group and there is no change in the imidazole ring that is fused.

Pentoxifylline

It is used as a drug to treat muscle pain in people with peripheral artery disease. It comes under the group of vasoactive drugs that improve peripheral blood flow and thus enhance peripheral tissue oxygenation. It is also known as Trental. The mechanism by which trental achieves this effect has not been identified yet it follows some factor that improve the red blood cell flexibility and contribute to the decrease in blood viscosity. Pentoxifylline regulates immunologic activity by stimulating cytokine production (Figure 7).

Functional groups in Pentoxifylline

As comparing with other derivatives this compound contains same as the caffeine, theobromine and other compounds but it contains ketone group with a hydrocarbon chain that made a bond with the nitrogen atom which is an amide. In the imidazole ring the hydrogen atom is substituted with $-CH_3$ group.

Aminophylline

Aminophylline is a compound of bronchodilator theophylline with ethylenediamine with a ratio of 2:1. The ethylenediamine increase the solubility, and the aminophylline is commonly found as a dihydrate. It is an established bronchodilator, is also claimed to be an effective diuretic and anti-inflammatory agent and causes an increase in gastric secretion. But the data to support these contentions are adequate [13].

Aminophylline has shown a few characteristic as a body fat

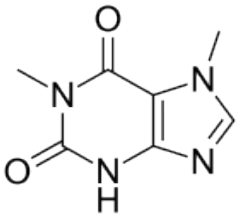

Figure 5: Paraxanthine.

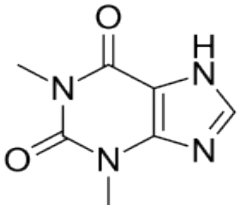

Figure 6: Theophylline.

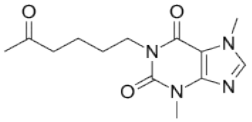

Figure 7: Pentoxifylline.

reducer when applied as a topical cream. It is highly soluble in water comparatively than theophylline. It is a White or slightly yellowish granules or can be a powdered, having a small degree of ammoniacal smell and bitter in taste. Upon exposure to atmosphere air, it moderately loses ethylenediamine and absorbs carbon dioxide with the liberation of free theophylline. Its solutions are alkaline. 1 g dissolves in 25 mL of water to give a clear solution; 1 g dissolved in 5 mL of water crystallizes upon standing, but once again dissolves when a small amount of ethylenediamine is added and it is insoluble in alcohol and in ether (Figure 8).

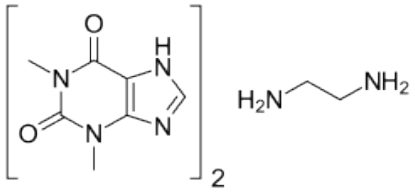

Figure 8: Aminophylline.

Functional groups in aminophylline

Theophylline and aminophylline both are similar but with an added one more molecule of theophylline with an ethylenediamine. This compound contains a functional group of theophylline that is two amide groups and an imine.

IBMX (3-isobutyl-1-methylxanthine)

3-Isobutyl-1-methylxanthine is a potent cyclic nucleotide phosphodiesterase inhibitor; due to this action, the compound increases cyclic AMP and cyclic GMP in tissue and thereby activates cyclic nucleotide regulated protein kinases. It is a nonselective adenosine receptor antagonist and does not inhibit PDE8 or PDE9 (Figure 9) [14].

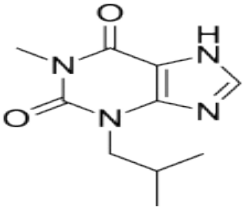

Figure 9: 3-Isobutyl-1-methylxanthine.

Functional groups in IBMX

As in the other methylxanthine derivatives IBMX has two amide groups, an imine group and keto groups that are incorporated. At one position of nitrogen methylpropyl substituted that gives the structural difference.

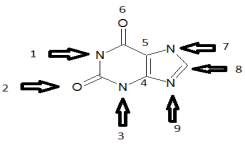

Figure 10: Different positions of the xanthine compound.

Effects of Functional Groups

The effect of the functional groups depends upon the substitutions that are present in different positions of the xanthine compound. Different effects that are exhibited by the substitution are given below (Figure 10).

- If the substitution takes place in position 1, it is responsible for the high affinity and selectivity towards adenosine receptor sites [15].
- If there is substitution at position 3 it can increases bronchodilator effect [16,17].
- Substitution in position 7 decreases both adenosine receptor antagonism and bronchodilator potency [18].
- Substitution at position 9 leads to reduced adenosine receptor affinity [19,18].
- Substitution at position 8 improves adenosine antagonism and selectivity towards A1 receptors [20,21].

Methylxanthine has characteristic feature of inhibition of adenosine receptors that concludes increased release of hormones such as dopamine and serotonin.

In spite of the positive effects, that are the antioxidant properties of methylxanthine may derive their pharmacological activities. Generally for different mechanisms are proposed to mediate the pharmacological activity of methylxanthine at the cellular level, antagonism of adenosine receptors, phosphodiesterase inhibition, modulation of GABA receptor action, and regulation of intercellular calcium levels [22,23].

Caffeine and theophylline are effective inhibitors of adenosine receptors in the human brain. Still theophylline and paraxanthine were suggested to have considerably more affinities than caffeine for the adenosine A_1, A_{2A} and A_{2B} receptors. Theobromine was stated to have specifically lower affinity than caffeine for A_1 and A_{2A} receptors [22]. Caffeine, theobromine and theophylline are considered comparatively weak competitive inhibitors. But theophylline is expected to have more potent inhibitor than caffeine. Adenosine receptors are categorized in terms of their capacity to decrease or increase intracellular cAMP concentration [22,24-27]. cAMP is an important messenger playing a basic roles in cellular responses to many neurotransmitters and hormone [22,28].

Phosphodiesterases inhibition was proposed to substantiate the bronchodilator effect of theophylline used for the treatment of asthma [22,29]. By the effects of methylxanthines in the regulation of GABA receptors, caffeine and theophylline were resulted to have impact on ion transport by their structure [22,30,31].

Different mechanism of action also may take place by the use of methylxanthine abundant supplements or medication [22,32].

Normally xanthine compound get excreted as urine by xanthine oxidase is an enzyme that contains molybdenum atom, also coordinated by terminal oxygen, sulfur atoms and a terminal hydroxide (2 molybdenum atoms, and 8 iron atoms bound per enzymatic unit). This enzyme generate reactive oxygen elements and it has the ability to catalyze hypoxanthine to xanthine and on further catalytic oxidation of xanthine is converted into uric acid. This uric acid gets filtered by kidneys and passes out as urine (Figure 11).

Conclusion and Discussion

Finally this paper can be concluded that it gives an understanding about the studies on the effect of functional groups and the importance of Methylxanthine derivatives. Especially caffeine that has deceased

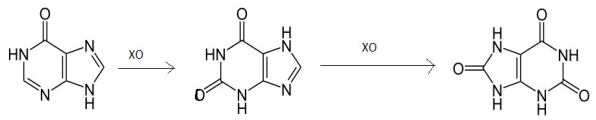

Figure 11: Xanthine is converted into uric acid.

level of toxicity when it is consumed in lesser amount but illness and side effect do arise when it is consumed in larger quantity that is more than 400 mg per day. Recently studies are aiming to determine the structural activity and physiology of methylxanthine drugs. Further technological development and research methodologies can provide lot more deeper knowledge of these derivatives.

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Author Declaration

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us.

We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property. We understand that the Corresponding Author is the sole contact for the Editorial process.

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