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# Biochemical Changes and Fatigability in Albino Rats after Oral Administration of Adenosine Triphosphate

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***Authors' contributions***

*This work was carried out in collaboration between all authors. Authors SVK, SB and GSK designed the study, wrote the protocol and supervised the work. Authors SB, SVK, KH and RM carried out all laboratories work and performed the statistical analysis. Author RM managed the analyses of the study. Authors SVK, RM and KH wrote the first draft of the manuscript. Authors SVK, RM and KH managed the literature searches and edited the manuscript. All authors read and approved the final manuscript.*

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## ABSTRACT

**Objective:** The study was undertaken to evaluate the biochemical changes and fatigability in albino rats after oral administration of adenosine triphosphate (ATP).
**Study Design:** Animal experimental study.

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**Place of Study:** Department of Biochemistry and Pharmacology, S. Nijalingappa Medical College, Navanagar, Bagalkot-587102, Karnataka, India.
**Methods:** Twelve Swiss albino rats of either gender weighing between 200 to 300 gm were taken. Animals were grouped randomly into two groups consisting of 6 rats each. Group –I received distilled water (5 ml/kg body weight) and Group-II ATP orally at the dosage of 60mg/kg body weight for 8 days. On 8$^{th}$ day of experiment, all animals were evaluated for extent of physical fatigue by using exhaustive swimming test. The blood samples were collected and blood sugar, urea, uric acid, hsCRP, total cholesterol and triglyceride were measured.
**Results:** There was a significant ($p<0.05$) increase in serum uric acid, blood sugar and urea in Group- II as compared to Group- I.
**Conclusion:** Oral administration of ATP may lead to hyperglycaemia, hyperuricemia and dyslipidaemia.

*Keywords: Adenosine triphosphate; hyperglycemia; hyperuricemia.*

## 1. INTRODUCTION

It is well established that adenosine-5′-triphosphate (ATP) is involved in all aspects of biosynthesis in cells and acts as the primary intracellular energy source. Extracellular ATP and its metabolites are involved in regulating a variety of biological processes like cardiac function, neurotransmission, liver glycogen metabolism, as cofactor for muscle contraction and platelet aggregation, which are primarily mediated through purinergic membrane receptors [1,2,3]. ATP has also been proposed as a mediator of vasodilation during ischemia, hypoxia, and exercise [4,5].

Substantial concentration of ATP is present in a number of foods like meat, soya, mushrooms and in breast milk [6-12]. Furthermore, capsules containing ATP are currently available in market as oral supplementation and also used for the treatment of low back pain of muscular origin [13]. It has to face a number of challenges before being used by the human body. The large molecular weight, the negative charge at physiological pH (pH 7.4), and the lack of known nucleotide transporters makes the intact ATP absorption difficult from outer cell membrane of small intestine. The enzyme ecto-nucleoside triphosphate diphosphohydrolase present on the luminal side of enterocytes will dephosphorylate ATP via ADP (Adenosine diphosphate) to AMP (Adenosine monophoshate). AMP in turn, is further degraded by ecto-5'-nucleotidase and alkaline phosphatase to adenosine [14]. Adenosine can be taken up into the enterocytes of the intestinal wall. This occurs through concentrative or equilibrative nucleoside transporters [15] on the baso-lateral side of enterocytes. Adenosine is taken up by erythrocytes, provided adenosine is released intact into the vascular bed and will come in contact with erythrocytes [16,17,18]. Then it will quickly enter into liver. In liver, adenosine will be broken down to uric acid by the enzymes adenosine deaminase and xanthine oxidase [19].

Effectiveness of oral ATP administration in sports is not well established, but usage is common for body building. Oral ATP supplements have shown beneficial effects in some but not in all studies examining physical performance [13]. Arts ICW et al showed that, a single dose of orally administered ATP is not bioavailable [13]. Studies have shown bioavailability of oral ATP is limited. The identification of a number of nucleoside transporters in the small intestine further suggested that orally administered ATP may be absorbed and utilized by the human body [18].

On the other hand, increase uric acid after release of ATP in the proximal part of the small intestine suggest that ATP or one of its metabolite is absorbed and metabolized, similar results were also observed by Coolen EJCM et al. ATP administered orally does not increase ATP concentrations in the blood [13]. It does not appear to have dangerous side effects in healthy individuals, but an increase in uric acid in the blood could increase the risk of gout [13,20].

Hyperuricemia may lead to gout and it is an independent risk factor for Diabetes mellitus, Dyslipidemia, Cardiovascular complications like coronary artery disease and stroke [21]. Most of studies have shown ATP administration leads to hyperuricemia, but not mentioned about other biochemical parameters, hence the present study was undertaken to know the changes in biochemical parameters like serum uric acid, urea, random blood sugar (RBS), serum

triglyceride (TGL), serum total cholesterol (TC), high sensitive C reactive protein (hsCRP) and fatiguability, in albino rats after oral administration of ATP.

## 2. MATERIALS AND METHODS

After obtaining clearance from Institutional Animal Ethics committee and animal regulatory body of India, twelve Swiss albino rats of either gender were selected from the central animal house of S Nijalingappa Medical College, Bagalkot, Karnataka, India.

Animals were randomly grouped into two groups, six animals in each. Distilled water 5 ml/kg body weight, was administered orally to Group I rats (Control group), and ATP 60 mg/kg body weight was administered orally for Group II rats (Experimental group). No protocol related procedures were undertaken before taking animal ethics committee approval. All procedures carried out in the study were as per CPCEA guidelines. Selected animals were examined and screened for general health condition including vital parameters. All the animals were acclimatized to laboratory for one week before starting the study. The animals were housed under standard laboratory conditions maintained at 25±5℃ and exposed to 12 hr dark and 12 hr light cycle and fed with standard pellet diet and water ad libitum. Group I and group II animals received distilled water and ATP orally for seven days respectively.

On the 8$^{th}$ day of experiment, all animals were evaluated for extent of physical fatigue by using exhaustive swimming test, using a cylindrical glass container, containing water at 25℃. Immobility time i.e. time taken by the animal to reach a stage where it makes only those movements required to keep its head above water is measured in minutes using stop watch. Then blood samples were collected under aseptic precautions. Serum uric acid, urea, RBS, TGL, TC, hsCRP were measured. All the biochemical parameters were estimated using STATFAX 3300, semi-auto analyser and kits were supplied by the BIOSYSTEMS Pvt Ltd.

All values were expressed in mean± SD. The data was statistically analysed using unpaired 't' test, $p<0.05$ was considered as statistically significant.

## 3. RESULTS

There was no statistically significant difference in body weight (p=0.978) and swim time (p=0.204) between control rats and rats fed with oral ATP (Table 1).

**Table 1. Weight and swim time in control and experimental groups**

| Parameter | Group | Mean±SD | t | p |
|---|---|---|---|---|
| Weight | I | 163.0±31.7 | 0.02 | 0.978 |
| (grams) | II | 162.5±30.7 | | |
| Swim time | I | 2.5±0.7 | 1.35 | 0.204 |
| (minutes) | II | 2.1±0.0 | | |

*Group I = Rats administered distilled water*
*Group –II= Rats administered oral ATP 60 mg/kg body weight*

Table 2 shows the biochemical parameters in control group and experimental group. All the biochemical parameters serum uric acid (p=0.000), Urea (p=0.004), RBS (p=0.000), were increased to statistically significant levels, in rats administered with oral ATP as compared to control albino rats. The other parameters like TGL (p=0.68), TC (p=0.89), hsCRP(p=0.798) were also increased in rats with oral ATP administration compared to control group, but it was not statistically significant.

## 4. DISCUSSION

In the present study there was significant increase in serum uric acid, urea and random blood glucose in albino rats fed with ATP, but there was no significant increase in strength. In rats chronic oral administration of ATP at 5 mg/kg/day increased portal vein ATP concentration and nucleoside. uptake by erythrocytes which resulted in an increase in ATP synthesis in the erythrocytes [22]. Animal and human study conducted by Jäger R et al. concluded that oral ATP administration can increase post-exercise blood flow, hence can be effective during exercise recovery [13]. Long-term oral administration of ATP has been shown to increase both the uptake and synthesis of ATP in the erythrocytes of rodents [22]. Animal studies reporting alterations in cardiac, vascular and pulmonary function after 30 days of oral ATP supplementation, also found no increase in systemic concentrations of plasma or erythrocyte ATP [22,23]. However, the concentration of ATP in plasma taken from the portal vein of rats increased rapidly up to a 1000-fold after instillation of ATP in the small intestine [22]. Oral ATP administration has been shown to improve muscular function. This is linked to accelerate recovery in people with acute and subacute lower back pain by improving muscular cell

function and increased blood flow [24]. Rathmacher JA et al. [25] in their study, supplementation with 400 mg ATP/d for 15 days tended to reduce muscle fatigue and improved participant's ability to maintain a higher force output at the end of an exhaustive exercise bout. In the study by Jordan et al. [26] no changes in whole blood and plasma ATP concentrations were detected, but the dosages administered were 225 mg or less. Wilson JM et al in their 3-phase randomized, double-blind, and placebo- and diet-controlled study showed that, oral ATP supplementation may enhance muscular adaptations following 12-weeks of resistance training, and prevent decrements in performance following overreaching. No statistically or clinically significant changes in blood chemistry or haematology were observed (Wilson JM et al. [27]). In an experimental study, to investigate anaerobic performance by Jordan et al.[26] three groups of nine healthy men received enteric coated ATP (150 or 225 mg) for 14 days. Physical performance and muscular strength were positively affected, although no significant differences were observed in whole blood and plasma ATP concentrations between the ATP and placebo groups [26].

Arts ICW et al. [13] in their study showed that the ATP is not orally bioavailable; also they found increased levels of serum uric acid. Hyperuricemia may also lead to progressive renal insufficiency, which leads to increase in urea also. Similar results were found in the present study. In animal studies by Kichenin et al. rats were injected with 10 mg/kg/day of ATP into the jejunum. Some of the molecules of ATP which are regenerated can be absorbed from the intestinal lumen and secreted into the portal vein [22,23]. ATP, adenine, inosine, adenosine, AMP, ADP and uric acid concentrations were increased in plasma [12]. Whereas, in humans [20], no changes in plasma ATP or metabolites were detected in the systemic circulation, the concentration of adenine, inosine, adenosine, adenosine monophosphate (AMP) and uric acid in plasma from the portal vein were increased. The authors concluded that these purine nucleosides can be absorbed from the intestinal lumen and secreted into the portal bloodstream [18].

In Maastricht University pilot-studies, experiments were performed to investigate the effects of oral ATP administration when ATP was ingested either dissolved in water or as enteric coated capsules [12]. These pilot studies showed a possible rise in blood uric acid concentration, but not ATP after oral ATP administration [12]. In a study by FoxI H et al. neither ATP nor adenosine concentrations were increased, suggesting that instead of being used for ATP synthesis in the erythrocytes, orally administered ATP is degraded to uric acid by xanthine oxidase, an enzyme which is expressed mainly in the liver and in endothelial cells of blood vessels [12,19], in the current study also there was no difference in swimming time between control and orally ATP fed rats but there was significant rise in serum uric acid in rats fed with oral ATP.

Hyperuricemia has been proposed as one of the risk factors for diabetes, but the epidemiologic studies have mixed results [28]. Elevated serum uric acid on its own has been linked to other gout-related conditions such as metabolic syndrome, insulin resistance, renal disease and hypertension [29,30]. Hyperuricemia has also

**Table 2. Biochemical parameters in control and experimental groups**

| Biochemical parameter | Group | Mean±SD | t | p |
|---|---|---|---|---|
| Uric acid (mg/dl) | I | 2.2±0.9 | 19.22 | 0.000 |
| | II | 4.5±0.1 | | |
| Urea (mg/dl) | I | 30.3±2.1 | 3.74 | 0.004 |
| | II | 37.3±3.9 | | |
| TGL (mg/dl) | I | 69.8±7.3 | 0.14 | 0.68 |
| | II | 71.0±1.1 | | |
| TC (mg/dl) | I | 45.7±1.5 | 0.13 | 0.89 |
| | II | 46.0±5.4 | | |
| RBS (mg/dl) | I | 73.1±6.0 | 14.24 | 0.000 |
| | II | 192.1±19.5 | | |
| hsCRP (µgm/L) | I | 1.3±0.8 | 0.26 | 0.798 |
| | II | 1.4±0.9 | | |

*TGL: Triglyceride; TC: Total cholesterol; RBS: Random blood sugar; hsCRP: High sensitive C- reactive protein*

been linked to atherosclerosis and diabetes [31]. Several studies have observed a positive association between serum uric acid levels and diabetes [28,32-37]. Pathophysiologic links between hyperuricemia, insulin resistance, and prediabetes have not been clearly established and are under investigation [28,38]. Krishna E et al. assessed the association between serum uric acid level and incidence both of type 2 diabetes and prediabetes, and their study suggested that hyperuricemia can be a useful predictor of diabetes mellitus and concluded urate concentration as an inexpensive marker for assessing the risk of future incident type 2 diabetes and diabetes-related outcomes in nonobese individuals [28]. Krishna E et al. in their cohort study among male US veterans with gout and no prior evidence of diabetes showed that in the descriptive analysis hyperuricemia among gout patients were associated with a significantly higher risk of developing diabetes compared to controls. They identified that hyperuricemia as a significant risk factor for diabetes, and medical interventions for hyperuricemia have the potential to reduce the risk of diabetes among patients at risk [39]. In a prospective cohort study of middle-aged and elderly Chinese patients, elevated serum uric acid was associated with a significantly increased risk of diabetes [40]. Moreover, a large meta-analysis of 11 cohort studies found that serum uric acid levels were associated with a higher risk of developing type 2 diabetes [41]. In the present study also, there was significant increase ($p<0.000$) in random blood glucose in rats fed with oral ATP, who have elevated uric acid level, than control group. Some studies have suggested that diabetics, especially those recently diagnosed, tend to have lower serum uric acid than prediabetic and normoglycemic patients [28,35].

Increased serum uric acid levels have been reported to be associated with dyslipidemia [42], and cardiovascular diseases [43-45]. There is positive correlation between serum uric acid, total cholesterol, and triacylglycerol [46]. Conenet et al. [47] and Schachter [48] research data indicated that serum triglyceride was markedly associated with hyperuricemia. In the current study there is statistically significant increase in uric acid in rats fed with oral ATP but the increase in TC and TGL, is not statistically significant.

Increased serum uric acid in humans is also associated with systemic inflammation [49], endothelial dysfunction [50], hypertension [51], CVD, and CVD mortality [52]. S. Kaptoge et al. demonstrated that hsCRP is also an inflammatory marker and independent predictor of CVD such as coronary heart disease, ischemic stroke, and vascular and non-vascular mortality [53]. In the present study there is significant increase in uric acid in rats fed with oral ATP and also increase in hsCRP but it is not statistically significant.

High uric acid concentrations have also been associated with beneficial health effects [12]. Epidemiological studies have shown that healthy subjects with high uric acid concentrations are at a reduced risk for developing Parkinson's disease [54,55]. Furthermore, patients with multiple sclerosis are known to have lower uric acid concentrations than healthy persons, and raising the uric acid concentration by pharmacological means has been the subject of recent investigation [56]. Although increasing the uric acid concentration pharmacologically using ATP pellets might have benefits for certain individuals, these have to be weighed against increased risks of gout and possibly DM and cardiovascular disease [57-59].

The limitations of the present study were the short duration, and less biochemical parameters were estimated due to difficulty in collecting the blood sample. Further long term human studies are required to emphasize and substantiate the current results.

## 5. CONCLUSION

In conclusion ATP supplementation may lead to hyperuricemia, hyperglycemia and their complications without much beneficial effects.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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