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RESEARCH ARTICLE

Bupropion Improves Biochemical Parameters of Ethanol Exposure in Rats

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ABSTRACT

Today, alcohol intake is a significant factor in many diseases primarily digestive system disorders. Despite dopamine agonists for helping to heal on alcohol-induced damages was known, the effects of bupropion on ethanol-induced varying biochemical parameters were not clarified completely. This study was conducted to assess the effects of bupropion on some changing biochemical parameters due to ethanol treatment. Rats were administered with 56% ethanol twice a week for four weeks and then bupropion was orally administered in doses of 30 and 60 mg/kg for 7 days. At the end of the study, it was found that bupropion reversed the values of aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), urea, creatinine, total protein, and glucose changed by ethanol. Study findings proved that bupropion improved effectively the changed biochemical parameters due to alcohol administration.
Keywords: Biochemical parameters, bupropion, ethanol, rat

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Bupropion Etanole Maruz Kalan Ratlarda Biyokimyasal Parametreleri İyileştirir

ÖZ

Günümüzde alkol alımı sindirim sistemi hastalıkları başta olmak üzere birçok hastalığın önemli bir etkenidir. Dopamin agonistlerinin alkol kaynaklı hasarlar üzerinde iyileşmeye yardımcı olduğunun bilinmesine karşın, bupropionun etanol kaynaklı değişen biyokimyasal parametreler üzerindeki etkileri tam olarak açıklığa kavuşturulmamıştır. Bu çalışma etanol uygulaması ile değişen bazı biyokimyasal parametreler üzerinde bupropionun etkisini değerlendirmek için gerçekleştirildi. Çalışmada ratlara haftada iki kez dört hafta süreyle % 56 etanol uygulaması yapıldı ve sonrasında bupropion 30 ve 60 mg/kg dozlarda yedi gün süreyle oral olarak uygulandı. Çalışma sonunda bupropionun etanol ile değişen aspartat aminotransferaz (AST), alanin aminotransferaz (ALT), alkalin fosfataz (ALP), üre, kreatinin, total protein ve glukoz değerlerini tersine çevirdiği belirlendi. Çalışma bulguları alkol uygulaması ile değişen biyokimyasal parametreleri bupropionun etkili bir şekilde iyileştirdiğini göstermiştir.
Anahtar Kelimeler: Biyokimyasal parametreler, bupropion, etanol, rat

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INTRODUCTION

Alcohol consumption causes damages on various tissues primarily upper parts of digestive system and liver (Aihara et al. 2003; Behrman, 2005). Continuous and excessive alcohol intake increases permeability of intestinal mucosa and produces excessive acetaldehyde that is a reactive ethanol metabolite (Fisher et al. 2010). Despite biochemical parameter indicators such as serum gamma glutamyl transferase (GGT), aspartate aminotransferase (AST), alanine aminotransferase (ALT) and erythrocyte mean cell volume (MCV) entailing limiting accuracy they were used in diagnosis of alcohol consumption (Sharpe et al. 1996). Moreover, it was reported in experimental study that biochemical parameters associated with alcohol intake went out of normal levels (Hamed 2011, Ozbayer et al. 2014).

It was reported that antidepressant medicines used to treat psychiatric illnesses successfully prevent some alcohol induced diseases (Andersen 1984, Shrivastava et al. 1985). Bupropion is a medicine blocks dopamine and noradrenalin reuptake and has non-competitive antagonistic effect to central nicotinic acetylcholine receptors. Besides using depression treatment, it was reported that bupropion helps to treat ulcer (Dedeoğlu et al. 2011). But, a study that shows the effect of bupropion on biochemical parameters was not found. For this reason, it was aimed to determine the effect of bupropion on biochemical parameters in alcohol administered rats.

MATERIAL and METHODS

Bupropion HCl used in study was purchased from GlaxoSmithKline (Istanbul, Turkey), and ethanol of 98% high purity from Sigma-Aldrich (MO, USA). Other chemicals, at high purity, to be used to determine parameters of analysis were purchased from commercial companies.

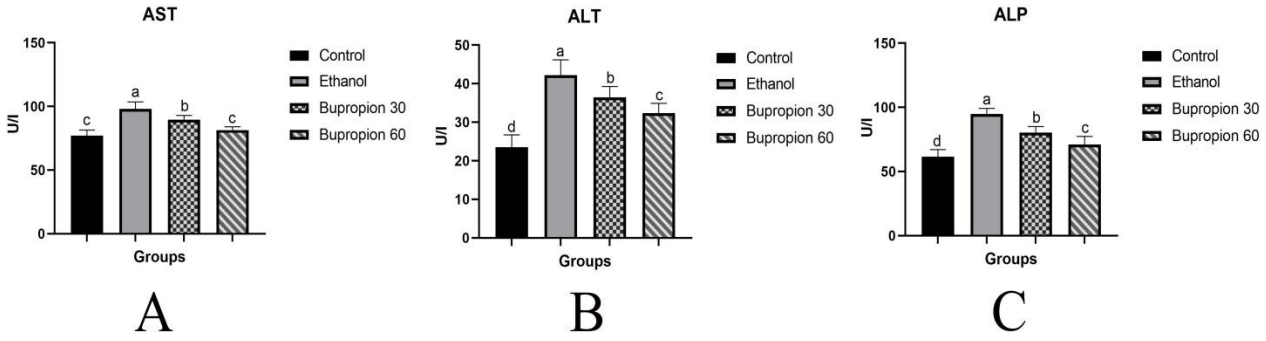
In this study, 2 months (180-200 g) 24 Sprague Dawley male rats were obtained from Afyon Kocatepe University Experimental Animal Application and Research Centre. During experiment, treatments applied to animals were conducted in accordance with universal ethical principles and by the approval of Afyon Kocatepe University Experimental Animal Local Ethics Committee (Ethical number: 49533702/76). Care and feeding of the rats were conducted at 22±2°C room temperature, 55-60% humidity and with a photoperiod of 12:12 hours. The rats in working group were fed with standard rodent and fresh drinking water ad libitum. Moreover, animals were kept without food before 24 hours of alcohol treatment.

Ethanol (Ji et al. 2019) and bupropion (Abuohashish et al. 2015) doses to be used in experimental phase were determined in accordance with the study conducted as before. Animals were divided as control group, alcohol group, group treated with 30 mg/kg bupropion and group treated with 60 mg/kg bupropion, into 4 groups each consisting of 6 male rats. After fasting of 12 hours, rats were administered orally with 56% (8 g/kg) ethanol two times a week. Normal and model groups were also orally administered with physiological saline water following same protocol. After four weeks, bupropion was administered once a day, over a seven days period and after 2 hours of last administration animals were taken under general anaesthesia with isoflurane and necessary blood samples were collected. To obtain plasma from blood samples, blood was centrifuged at 600 g for 15 minutes. After centrifuge the plasma obtained were stored until they were analysed at -20°C.

In order to determine the values of biochemical parameters AST, ALT, ALP, total protein, glucose, blood urea (BUN), and creatinine the kits purchased from commercial companies (Human Diagnostics, Wiesbaden, Germany) and visible spectrophotometer (Tokyo, Japan) to measure these parameters were used.

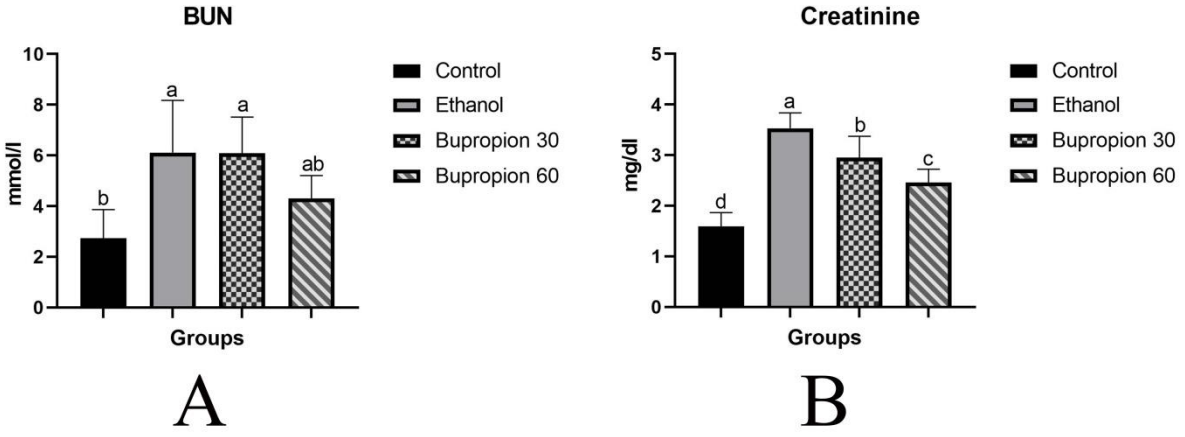
RESULTS

It was found that in rats administered with ethanol the plasma AST, ALT, and ALP levels were higher compared with control group, on the other hand levels were decreased compared with alcohol group depending on increased bupropion treatment ($p<0.001$; Figure 1A-C). It was found that, plasma total protein ($p<0.01$; Figure 3B) in animals administered with ethanol levels were decreased compared with control group, on the other hand the levels of BUN ($p\leq0.001$; Figure 2A), creatinine ($p<0.001$; Figure 2B) and glucose ($p<0.001$; Figure 3A) were increased. It was found that these values were decreased in groups administered with bupropion depending on increased dose compared with alcohol group and approximated to control.



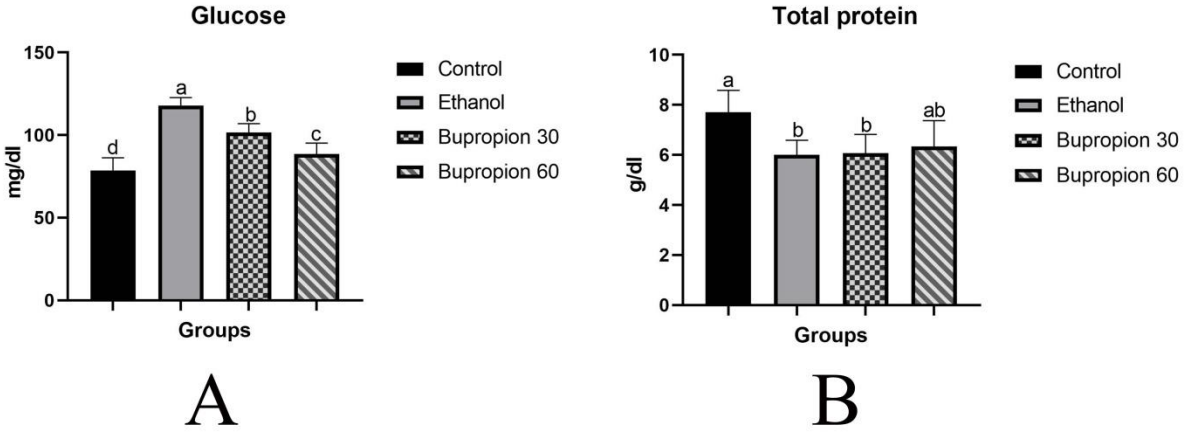
Şekil 1: Alkol ile 30 ve 60 mg/kg dozda bupropionun ratlara uygulamasının AST, ALT ve ALP düzeyleri üzerine etkisi. Veriler ortalama ± standart sapma olarak ifade edilmiştir. [a,b,c,d]: farklı harfleri taşıyan gruplar arasında önemlilik bulunmaktadır.

Figure 1: The effect on AST, ALT, and ALP levels of bupropion administration in rats administered with alcohol in doses of 30 and 60 mg/kg. Data were expressed as average ± standard deviation. [a,b,c,d]: the differences among groups bearing different letters are significant.



Şekil 2: Alkol ile 30 ve 60 mg/kg dozda bupropionun ratlara uygulamasının BUN ve kreatinin düzeyleri üzerine etkisi. Veriler aritmetik ortalama ± standart sapma olarak ifade edilmiştir. [a,b,c,d]: farklı harfleri taşıyan gruplar arasında önemlilik bulunmaktadır.

Figure 2: The effect on BUN and creatinine levels of bupropion administration in rats administered with alcohol in doses of 30 and 60 mg/kg. Data were expressed as average ± standard deviation. [a,b,c,d]: the differences among groups bearing different letters are significant.



Şekil 3: Alkol ile 30 ve 60 mg/kg dozda bupropionun ratlara uygulamasının glukoz ve total protein düzeyleri üzerine etkisi. Veriler aritmetik ortalama ± standart sapma olarak ifade edilmiştir. [a,b,c,d]: farklı harfleri taşıyan gruplar arasında önemlilik bulunmaktadır.

Figure 3: The effect on glucose and total protein levels of bupropion administration in rats administered with alcohol in doses of 30 and 60 mg/kg. Data were expressed as average ± standard deviation. [a,b,c,d]: the differences among groups bearing different letters are significant.

DISCUSSION

Investigations made reveals that high exposure to alcohol increases the AST and ALT levels in blood (Halvorson et al. 1993). One of two enzymes ALT is more specific measure of alcohol induced liver damage. Because ALT is located primarily in liver while AST is found in various organs including heart, muscle, kidney, and brain. Very high levels of these enzymes (for example, 500 unit per liter) may indicate alcoholic liver disease (Peterson, 2004). When some experimental alcohol administration studies were investigated; it was reported that, following single dose of 10 mg/kg ethanol administration to rats significant increase in alcohol dehydrogenase level in blood and in AST, ALT and lactate dehydrogenase (LDH) enzyme activities was found (Hamed, 2011). In another study conducted similarly, it was reported that single dose of 75% ethanol (2.5 ml/kg) administration in rats increased serum AST, ALT and LDH levels (Ozbayer et al. 2014). In the study, it was found that, significant increase in AST, ALT and ALP levels in rats administered with ethanol was found and bupropion administration decreased these levels with increased alcohol administration. In the study conducted in line with other studies, this case shows that bupropion reduces negative effects of alcohol primarily on liver and other organs.

It was reported that, in the study where the urea synthesis, alanine elimination were investigated for the rats administered with acute low dose of (8-14 mmol/l, i.v.) ethanol and nitrogen conversion was investigated for satiated and fasted rats, the blood urea quantity was decreased in both cases (Jensen et al. 1991). In contrary to this, it was reported that, in the study where ethanol was given to rats in different concentrations (5, 8, 10, and 12 g/kg) for once a week, BUN and creatinine values were increased after four weeks (Tahir and Sultana 2011). Also, in this study, it was found that BUN and creatinine levels were increased and bupropion administrations reduced these increased levels. The increase in BUN and creatinine levels may be depend on these cytosolic enzymes to leak into circulatory system by the alteration of membrane permeability due to liver and kidney damage during ethanol administration. Bupropion potentially may have reduced these values by contributing to protection of cellular membrane integrity in tissues and preventing tissue damage.

Despite it is widely known that gluconeogenesis is suppressed by the ethanol the effect of alcohol intake on the blood glucose levels is controversial. Ethanol may have effect on liver both for glucose production and glucose consumption (Mokuda et al. 2004). In the study where the effects of ethanol on the glucose transporters (GLUT) and glucose use in rat brain were investigated the rats were given 3 g/kg ethanol before 4 hours of removal of cerebral cortical tissue and a decrease in GLUT number and protein content was observed in rats given ethanol compared with control group (Handa et al. 2000). Moreover, it was reported that as a result of short and long term ethanol exposure blood glucose concentrations, glucose intolerance and insulin resistance was increased and chronic alcohol consumption is an independent risk factor for type 2 diabetes development in some populations (Fowman 1988, Rachdaoui et al. 2003). In the study, it was observed

that glucose level was increased in groups administered with alcohol; on the other hand the increased level was reduced by bupropion administration. This situation may happen from regulatory effect of bupropion on glucose metabolism (Costello et al. 2010) and/or insulin secretion (el-Dakhakhny et al. 1996). It was reported that ethanol administration reduced serum total protein and albumin quantity, this case was resulted from decreased liver functionality depending on alcohol intake (Ahmed et al. 2002, Saravanan et al. 2006). In similar way, it was reported that, ethanol administration caused decrease in total protein quantity, an increase in total protein level was observed, even not statistically significant in rats administered with bupropion compared with alcohol group. This situation may be resulted from the improvement of stabilization of blood protein levels by bupropion administration and additionally of functional status of liver cells.

As a result, it was found that biochemical parameters have exceeded normal limits in rats administered with ethanol for four weeks, these parameters that were changed with alcohol approached to run their normal course by the bupropion administrations in doses of 30 and 60 mg/kg. We reached the conclusion that, the bupropion in addition to using as antidepressant may reduce alcohol induced tissue damage and it would be beneficial to consider this case in therapeutic approach.

Ethics Committee Information: The study was approved by Afyon Kocatepe University Ethics Committee (Ethical number: 49533702/76).

Conflict of interest: The author has declared that no competing interest exists.

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