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TIME-COURSE EFFECTS OF LOW-LEVELS ARSENIC ON ELECTROLYTES AND LIPIDS IN MALE ALBINO RATS

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ABSTRACT

This study was conducted to investigate the time-course effects of low levels of organic arsenic on electrolytes balance and lipid profiles in different organs of male rats. Animals were exposed to arsenic (As) as Dimethylarsenate (DMA) in their drinking water for 5, 10 and 15 weeks at doses 20 and 40 ppm. Lipids (Triacylglycerol (TAG), total cholesterol, phospholipids) and electrolytes (sodium, potassium, magnesium, calcium) levels were determined in the hepatic, renal, brain and cardiac tissues of experimental animals. Potassium significantly ($p<0.05$) increased in the hepatic, renal and cardiac tissues after 5 weeks exposure to 40 ppm arsenic. Significant ($p<0.05$) increase observed in hepatocytes calcium level was shown to be dose-dependent. While there was no observed significant ($p>0.05$) difference in hepatic and renal magnesium after 15 weeks exposure, magnesium significantly altered in the brain and cardiac tissues after 15 weeks. TAG concentration in most of the organs studied was significantly ($p<0.05$) altered after 5 weeks exposure to 20 ppm arsenic. Phospholipids in the renal and hepatic tissues were also significantly ($p<0.05$) decreased after 15 weeks of exposure to As. However, only in the renal tissues was hypocholesterolemia observed in 40 ppm groups at 5, 10 and 15 weeks of exposure. Our findings indicate exposure to progressively low-levels arsenic can result in electrolytes imbalance and dyslipidemia in different organs in rats.

Keywords: organic arsenate, lipids, electrolytes, renal, brain, hepatic, cardiac, tissues

INTRODUCTION

Arsenic is a metalloid, which possesses characteristics of both a metal and a non-metal and is widely distributed in the soil, water, air and rocks (Hong *et al*., 2014). Man's continuous activities mediate the efflux of this element into the atmosphere and environment thus increasing its availability and hence toxicity (Izah and Srivastav, 2015; Obinaju, 2009).Exposure to arsenic is mainly through food and drinking water (Mandal, 2017).

Current global estimates indicate that some 150 million people consume groundwater containing arsenic concentrations above the WHO-limit of 10µg/L (Ucuncu *et al*., 2018; Izah and Srivastav, 2015; Ravenscroft *et al*., 2009). The relative toxicity of arsenic depends primarily on the inorganic or anionic form, oxidation state, solubility, physical state and rates of absorption which can vary greatly in arsenic compounds; in general arsenic compounds can be ranked from highest to lowest toxicityin the following order: inorganic trivalent compounds > organic

trivalent > inorganic pentavalent compounds > organic pentavalent compounds > elemental arsenic (Gorby, 1988).

Occupational exposure to arsenic among workers in a glass plant in India whose blood arsenic were five times higher than in the control group was reported to lead to increased DNA damage in leukocytes (Liu *et al*., 2016; Vuyyuri *et al*., 2006). The genotoxicity of organic arsenic has also been thoroughly investigated (Eckstein *et al.,* 2017;Kuroda *et al*., 2004). Arsenic exposure has been linked with various types of cancer (Mandal, 2017; Monrad *et al*., 2017; Miller *et al*., 2002; Tseng *et al*., 1968), cardiovascular disease (Valko *et al.,* 2016; Abdul *et al.,* 2015; Afolabi *et al*., 2014: Nava-Acien *et al*., 2005), diabetes (Grau-Perez *et al*, 2017; Diaz-Villasenor *et al*., 2007), neurological disorders (Tyler and Allan, 2014; Valudnia *et al*., 2007) and dermal effects (Cohen *et al*., 2006), work is still on-going to discover the mechanism of action of arsenic in causing these deleterious effects.

In this study we investigated the time course effects of low level arsenic exposure on the electrolyte concentrations and lipids profile in some organs in male albino rats.

MATERIALS AND METHODS

Chemicals

Dimethylarsenate (DMA) used was obtained from Sigma chemicals company St.Louis, MO USA. Other reagents used were of analytical grade and were prepared using distilled water.

Animals

Adult male albino rats with an average weight of 150g, obtained from the Department of Zoology, University of Ibadan, Nigeria were used for this research. Rats were housed in plastic cages maintained at 25±2ºC and 12 hours light were given free access to food and water *ad libitum*.

Animals were grouped into nine (9) groups of five (5) rats each. Groups I, IV and VII served as control groups for 5, 10 and 15 weeks Dimethylarsenate (DMA) exposure respectively. Groups II, V and VIII were exposed to 20ppm arsenicas DMA for 5, 10 and 15 weeks respectively while groups III, VI and IX were given 40ppm arsenic as DMA. Animals were exposed to arsenic through their drinking water.

Sample Collection and Analyses

Animals were sacrificed under light diethyl ether anesthesia. Blood samples were collected from the abdominal artery into heparinized tubes while the kidney, brain, heart and liver tissues were harvested into physiological saline and then blotted dried. The blood samples were centrifuged at 4,000 rpm from 5 minutes to obtain the plasma (upper layer) used for analysis. Homogenate (10%) of the organs was obtained using 0.25M Sucrose. Chloroform-methanol mixture (2:1 v/v) was used to obtain the 10% homogenate used for lipid analysis according to the method described by Folch *et al.* (1957).

Biochemical analyses

Lipid indices such as triacylglycerols (TAG), cholesterol and phospholipids concentrations were determined in the lipid extracts using methods described by Bucolo and David, 1973; Allain *et al*. (1974) and Stewart (1980) respectively.

Briefly, TAG concentration was determined based on the enzymatic hydrolysis of triglycerides to glycerol and free fatty acids (FFA) by lipoprotein lipase (LPL). The glycerol is phosphorylated by adenosine triphosphate (ATP) in the presence of glycerolkinase

(GK) to form glycerol-3-phosphate (G-3-P) and adenosine diphosphate (ADP). G-3-P is oxidized by glycerophosphate oxidase (GPO) to form dihydroxy acetone phosphate (DHAP) and hydrogen peroxide. Cholesterol concentration was determined after enzymatic hydrolysis and oxidation of cholesteryl esters. The indicator quinonemine concentration is then measured spectrophotometrically which correlates to the concentration of cholesterol concentration in the sample.Phospholipids concentration was assayed based on complex formation between ammonium ferrothiocyanate and phospholipids.

Electrolytes which include sodium (Na^+), potassium (K^+), calcium (Ca^{2+}) and magnesium (Mg^{2+}) levels were determined using the methods described by Trinder (1951), Terri and Sesin (1958), Tietz (1995) and Chromya *et al*. (1973) respectively. Briefly, Na^+in the sample was precipitated as a triple salt, the excess uranium was then reacted with ferrocyanide to produce achromophore whose absorbance varies inversely with the concentration of Na^+present in the sample. Likewise, K^+ was determined after precipitation of the proteins, by using sodiumtetraphenylboron in an alkaline medium to produce a colloidalsuspension. The turbidity formed is proportional to K^+concentration in the sample, and was measuredspectrophometrically. Ca^{2+} reacts with Arsenazo 111{1,8-Dihydroxy-3,6-disulpho-2,7-naphthalene-bis (azo)-dibenzenearsonic acid} at neutralpH, to yield a bluecoloured complex whose intensity is proportional to the Ca^{2+} concentration in the sample, whileMg^{2+} forms a coloured complex when treated with xylidyl blue in alkaline solution. The intensity of the colour is proportional to the concentration in the sample.

Statistical Evaluation

Values are expressed as mean ± S.E.M. The data were statistically analyzed using analysis of variance (ANOVA). The level of homogeneity among the groups was tested using Duncan's multiple range test (DMRT). $P<0.05$ were considered to be significant.

RESULTS

In the hepatic tissues (Table 1), after 15 weeks of exposure, there was no significant difference in the total cholesterol concentration; however, our results revealed that chronic exposure to 40ppm arsenic results in a significant reduction in TAG and phospholipids levels. In the renal tissues, TAG and cholesterol concentrations were significantly reduced after 5 weeks exposure to 40ppm arsenic(Table 2), however, all lipids indices measured in this study were significantly reduced in the renal tissues after 15 weeks of exposure to arsenic as shown in Table 2. Results indicated 20 and 40ppm doses of arsenic had no significant effect on cholesterol and phospholipids levels of the brain after 15 weeks although TAG level was decreased significantly with 54.4% when compared with the control group (Table 3). In the cardiac tissues (Table 4) while phospholipids level was significantly increased in 40ppm group after 15 weeks exposure to the toxicant, TAG level was decreased.

From Table 5 results showed significant increase in Na^+ level (40ppm for 15 weeks) and Ca^{2+} level (all through the course of exposure) in the hepatic tissues. Mg^{2+} and K^+ levels were decreased after 10 weeks and 15 weeks respectively. In the renal tissues, all electrolytes studied except Mg^{2+} decreased significantly after 15 weeks of exposure. In the brain tissues, Na^+, K^+ and Mg^{2+} were

significantly increased however, the increase observed in Na^+ and K^+ levels was from 10 weeks exposure while Mg^{2+} was increased after 15 weeks (Table 7). In Table 8, Ca^{2+} level of the cardiac tissue decreased in 40ppm exposed group. Although K^+ increased for the first 10 weeks of exposure, after 15 weeks there was a significant reduction of 26.7% and 60% in 20 and 40ppm groups respectively. There was no observable pattern of change for cardiac Mg^{2+}on exposure to arsenic.

Duration	**Group**	**Total Cholesterol**	**Triacylglycerol (TAG)**	**phospholipids**
5 weeks	Control	12.39±0.96^a	4.38±0.27^a	18.09±1.38^a
	20ppm	11.08±0.96^a	8.60±0.21^b	16.14±1.21^a
	40ppm	8.78±0.48^b	12.80±0.84^c	17.33±1.14^a
10 weeks	Control	14.68±1.33^a	7.05±0.59^a	15.43±0.68^a
	20ppm	13.30±0.63^b	8.99±0.43^b	19.45±2.16^b
	40ppm	16.89±1.72^a	7.07±1.00^{ab}	21.74±0.82^b
15 weeks	Control	11.74±1.09^a	6.20±0.57^a	22.87±0.78^a
	20ppm	13.57±2.03^a	6.76±0.24^a	18.16±2.06^b
	40ppm	11.62±0.88^a	4.01±0.14^b	5.95±1.06^c

Values are expressed as mean ± standard error of mean (S.E.M). Values with different superscript within the same column in the same group are significantly different ($p<0.05$).

Table 2: Effects of Arsenic on Renal Lipid Profiles (mg/g of organ)

Duration	Group	Total Cholesterol	Triacylglycerol (TAG)	phospholipids
5 weeks	Control	14.45±0.85^a	8.52±0.33^a	23.70±2.10^a
	20ppm	14.16±0.45^a	9.49±1.35^a	24.00±2.89^a
	40ppm	7.81±0.76^b	4.97±0.085^b	23.70±2.03^a
10 weeks	Control	20.92±2.87^a	9.68±0.66^a	18.56±1.01^a
	20ppm	13.95±0.93^b	8.79±0.35^{ab}	21.58±1.16^{ab}
	40ppm	15.08±0.58^b	9.33±0.91^{ab}	24.99±0.88^b
15 weeks	Control	29.71±1.54^a	12.73±0.50^a	24.92±2.01^a
	20ppm	15.73±4.11^b	9.59±0.47^b	18.33±1.77^b
	40ppm	17.50±0.90^b	9.33±0.91^b	10.16±0.83^c

Values are expressed as mean ± standard error of mean (S.E.M). Values with different superscript within the same column in the same group are significantly different ($p<0.05$).

Table 3: Effects of arsenic on lipid profiles of the brain tissues (mg/g of organ)

Duration	Group	Total Cholesterol	Triacylglycerol (TAG)	phospholipids
5 weeks	Control	12.21±0.53[a]	12.04±3.33[a]	27.99±3.48[a]
	20ppm	10.53±0.33[a]	7.90±0.52 [b]	31.94±2.25[a]
	40ppm	20.78±4.83[b]	6.36±0.52[b]	29.85±0.46[a]
10 weeks	Control	24.24±5.11[a]	10.12±1.72[a]	29.34±0.42[a]
	20ppm	18.44±2.61[a]	8.75±0.15 [a]	30.47±0.48[a]
	40ppm	14.92±1.86[a]	9.75±1.05[a]	30.22±0.49[a]
15 weeks	Control	22.42±2.23[a]	10.77±0.23[a]	28.54±1.64[a]
	20ppm	24.92±0.73[a]	13.84±2.34[a]	29.96±2.36[a]
	40ppm	23.27±0.70[a]	4.91±0.44[b]	24.96±2.36[a]

Values are expressed as mean ± standard error of mean (S.E.M). Values with different superscript within the same column in the same group are significantly different ($p<0.05$).

Table 4: Effects of Arsenic on Cardiac Lipid Profiles (mg/g of organ)

	Group	**Total Cholesterol**	**Triacylglycerol (TAG)**	**phospholipids**
5 weeks	Control	10.92±1.10[a]	6.38±0.36[a]	18.21±1.64[a]
	20ppm	9.31±0.43[a]	11.97±1.20 [b]	18.04±0.50[a]
	40ppm	12.54±1.29[a]	15.05±0.72[b]	19.55±1.37[a]
10 weeks	Control	9.95±0.46[a]	7.78±0.58[a]	15.02±0.65[a]
	20ppm	11.08±0.85[a]	7.73±0.31[a]	20.79±2.30[b]
	40ppm	9.51±0.27[a]	6.77±0.26[a]	20.69±0.75[b]
15 weeks	Control	11.97±0.56[a]	5.87±0.78[a]	20.25±1.30[a]
	20ppm	10.06±0.96[a]	5.79±0.97[a]	18.09±0.58[a]
	40ppm	10.45±0.50[a]	4.76±0.27[b]	28.20±1.44[b]

Values are expressed as mean ± standard error of mean (S.E.M). Values with different superscript within the same column in the same group are significantly different ($p<0.05$).

Table 5: Effects of arsenic on hepatic electrolytes

	Groups	Na^+ (mEq/g)	K^+ (mEq/g) $\times 10^{-2}$	Ca^{2+} (mg/g)	Mg^{2+} (mg/g)
5 weeks	Control	0.31±0.04^a	3.00±0.10^a	0.35±0.05^a	0.07±0.01^a
	20ppm	0.37±0.04^a	3.00±0.20^a	0.52±0.05^b	0.08±0.01^a
	40ppm	0.28±0.02^a	4.00±0.10^b	0.65±0.02^b	0.09±0.02^a
10 weeks	Control	0.28±0.14^a	3.00±0.40^a	0.34±0.05^a	0.15±0.01^a
	20ppm	0.34±0.02^a	4.00±0.04^c	0.66±0.07^b	0.10±0.01^b
	40ppm	0.49±0.04^b	4.00±0.05^c	0.69±0.06^b	0.11±0.01^b
15 weeks	Control	0.26±0.02^a	5.00±0.40^a	0.36±0.04^a	0.17±0.01^a
	20ppm	0.24±0.02^a	2.00±0.20^b	0.70±0.03^b	0.19±0.00^a
	40ppm	0.53±0.03^b	2.00±0.10^b	0.84±0.04^b	0.18±0.01^a

Values are expressed as mean ± S.E.M. values with different superscript within the same column in the same group are significantly ($p<0.05$) -different.

Table 6: Effects of arsenic on renal electrolytes

	Groups	Na^+ (mEq/g)	K^+ (mEq/g) $\times 10^{-2}$	Ca^{2+} (mg/g)	Mg^{2+} (mg/g)
5 weeks	Control	1.35±0.01^a	2.30±0.10^a	0.65±0.07^a	0.10±0.01^a
	20ppm	1.46±0.04^a	2.00±0.10^a	0.41±0.05^b	0.09±0.01^a
	40ppm	1.20±0.05^a	3.50±0.03^b	0.29±0.05^b	0.09±0.02^a
10 weeks	Control	0.89±0.04^a	3.40±0.30^a	0.41±0.02^a	0.15±0.03^a
	20ppm	0.99±0.02^a	3.30±0.10^a	0.37±0.09^a	0.12±0.00^b
	40ppm	0.78±0.03^a	3.90±0.01^b	0.31±0.07^a	0.12±0.00^b
15 weeks	Control	0.72±0.04^a	3.90±0.00^a	0.72±0.05^a	0.17±0.01^a
	20ppm	0.21±0.02^b	1.60±0.03^b	0.40±0.04^b	0.17±0.00^a
	40ppm	0.27±0.03^b	1.70±0.10^b	0.26±0.04^b	0.17±0.01^a

Values are expressed as mean ± S.E.M. values with different superscript within the same column in the same group are significantly ($p<0.05$) different.

Table 7: Effects of arsenic on electrolytes of the brain tissues

	Groups	Na^+ (mEq/g)	K^+ (mEq/g) $\times 10^{-2}$	Ca^{2+} (mg/g)	Mg^{2+} (mg/g)
5 weeks	Control	1.08±0.03[a]	2.70±0.10[a]	0.75±0.08[a]	0.07±0.01[a]
	20ppm	1.15±0.07[a]	2.90±0.10[a]	0.56±0.04[b]	0.07±0.00[a]
	40ppm	1.03±0.04[a]	3.00±0.10[a]	0.53±0.06[b]	0.08±0.01[a]
10 weeks	Control	0.89±0.04[a]	3.30±0.20[a]	0.40±0.03[a]	0.16±0.01[a]
	20ppm	1.17±0.08[b]	3.00±0.10[a]	0.57±0.06[a]	0.13±0.01[a]
	40ppm	1.11±0.09[b]	3.90±0.03[b]	0.39±0.11[a]	0.15±0.00[a]
15 weeks	Control	0.87±0.06[a]	3.20±0.10[a]	0.51±0.03[a]	0.15±0.01[a]
	20ppm	1.21±0.02[b]	2.10±0.10[b]	0.56±0.03[a]	0.17±0.00[b]
	40ppm	1.26±0.02[b]	1.80±0.10[b]	0.46±0.03[a]	0.17±0.01[b]

Values are expressed as mean ± S.E.M. values with different superscript within the same column in the same group are significantly ($p<0.05$) different.

Table 8: Effects of arsenic on cardiacelectrolytes

	Groups	Na^+ (mEq/g)	K^+ (mEq/g) $\times 10^{-2}$	Ca^{2+} (mg/g)	Mg^2 (mg/g)
5 weeks	Control	0.58±0.13[a]	2.40±0.10[a]	0.65±0.06[a]	0.08±0.01[b]
	20ppm	0.70±0.22[a]	2.80±0.20[b]	0.63±0.03[a]	0.05±0.00[a]
	40ppm	0.70±0.19[a]	3.20±0.10[b]	0.49±0.04[b]	0.09±0.01[b]
10 weeks	Control	0.88±0.11[a]	3.50±0.10[a]	0.50±0.04[a]	0.16±0.02[a]
	20ppm	0.61±0.15[a]	3.70±0.10[a]	0.54±0.09[a]	0.09±0.00[b]
	40ppm	0.81±0.13[a]	3.90±0.02[b]	0.33±0.99[b]	0.11±0.00[b]
15 weeks	Control	1.02±0.19[a]	3.00±0.40[a]	0.57±0.04[a]	0.10±0.00[a]
	20ppm	1.21±0.19[a]	2.20±0.10[b]	0.53±0.02[a]	0.18±0.00[b]
	40ppm	1.44±0.17[a]	1.20±0.10[b]	0.42±0.02[b]	0.18±0.00[b]

Values are expressed as mean ± S.E.M. values with different superscript within the same column in the same group are significantly ($p<0.05$) different.

DISCUSSION

Arsenic has been reported to cause oxidative stress thus induction of several reactive oxygen species (ROS) which ultimately leads to cell damage (Ghulam *et al.,* 2018; Chandrakar *et al.,* 2017; Vizcaya-Ruiz *et al.,*2009). Lipids are one of the most susceptible targets of free radicals (Mushtaq *et al*., 2017; Sanjib and Sajal, 2013;Rajani and Purnima, 2009). Epidemiological studies have associated arsenic exposure with elevated risks of hypertension (Grau-Perez *et al.,* 2017; Rahman *et al.,* 1999; Chen *et al.,* 1995), carotid atheroslecrosis, ischemic heart disease (Abdul *et al*., 2015; Hsueh *et al.,* 1998; Tseng *et al.,* 2003), and vascular disease mortality (Valko *et al*., 2016; Chen *et al.,* 1996).Studies have shown that arsenic treatment induced hepatic injury via alterations of lipid profiles with noticeable alterations in liver function. The results of this study showed that there was a significant ($p<0.05$) difference in the TAG, cholesterol and phospholipids levels at varying concentrations in the hepatic tissues which could be as a result of steatosis or ATP depletion supported by the findings of Gresser (1981); Liu and Waalkes (2008) whose findings indicated arsenic as a cause of change in liver fats due to ATP depletion. Cardiac TAG and phospholipids levels were significantly increased as a result of arsenic exposure from our study leading to hyperlipidemia which can result in cardiovascular diseases. Our findings support arsenic exposure to cause cardiovascular diseases as reported by Bambino *et al*. (2017);Valko *et al.* (2016); Balakumar and Kaur (2009); Wang *et al*. (2002). Diseased conditions of the liver and/or mal-absorbtion can lead to decreased levels of nutrients (Criqui, 1994). We observed hepatic hypocholesterolemia in rats exposed to arsenic after 5 weeks. This could be linked in part to malabsorption and alteration of membrane integrity as observed by decreased hepatic phospholipids levels after exposure for 15 weeks.

Electrolyte balance is necessary for normal functioning of cells and organs. Fluid and electrolyte homeostasis occurs when fluids and electrolytes balance is maintained within narrow limits despite a wide variety in dietary intake, metabolic rate and kidney function. Previous studies by Shafaq and Tabassum (2008), reported that cisplatin disturbed balance between oxidation and antioxidation mechanism which consequently affect the membrane electrolytes revealing that disturbance occur in plasma and membrane electrolytes in cisplatin treated rats. This present study showed exposure to DMA can cause Na^+ and K^+ ion imbalance in liver, kidney, brain and heart.

A significant decrease ($p<0.05$) in Na^+ in the renal tissues with both 20 and 40ppm during arsenic exposure for 15 weeks was observed when compared with the control group leading to hyponatremia as reported by Anand and Saxena (2015), which could be as a result of degeneration of the kidney tissue, caused by the attachment of DMA with the protein of the renal tubular epithelium as reported by Chandrakar *et al.* (2017); Schnellmann and Kelly (2008) and thus movement of ATPase from basolateral to apical membrane. This produces reactive oxygen species (ROS) which was reported to cause peroxidation of unsaturated fatty acids in biological membranes (Schnellmann and Kelly, 2008). This effect leads to decrease in membrane fluidity and membrane integrity which delocalizes the enzymes Na^+/K^+ ATPase which is involved in the transportation of the ion. This effect thus resulted in decreased reabsorption causing increased urinary loss of the ion (Ajai *et al*., 2013). This can cause electrolytes

imbalance as observed in our results.

The observed significant ($p<0.05$) decrease in K^+in the cardiac tissues at both 20ppm and 40ppm (15weeks) could cause the heart muscle not to relax between breath because K^+ is an essential ion required for this process. There could be decrease in the activity of some enzymes required in energy metabolism such as kinases and this could eventually lead to irregular heartbeat and there would be a decrease in the capacity of the heart to pump blood, because these processes require energy (Taber and Venes, 2009). High intracellular K^+ is essential for important metabolic functions which include protein biosynthesis by ribosome; there could be a disruption in the biosynthesis of protein by the cardiac cells (Anand and Saxena 2015).

In the hepatic tissues, Ca^{2+} concentration was significantly increased in all exposed groups while a significant ($p<0.05$) decrease was observed in the renal tissue (5 and 15weeks). This may be due to the impairment of either net electrolytes influx or hepatic/renal function as reported by Rogers *et al*. (2003) and disruption of the cell membrane permeability (Murray *et al*., 2000). The impairment in the flux of Ca^{2+} in the body could also pose a threat to muscle contraction, transmission of nerve impulses and in neuromuscular excitability (Malhotra, 1998). Reduced extracellular Ca^{2+} increases the irritability of nerve tissue, and very low levels may cause spontaneous discharge of nerve impulses leading to tetany and convulsions (Hays and Swenson, 1985; Malhotra 1998; Murray *et al*., 2000).

CONCLUSION

Results from this study showed that arsenic in form of DMA at 20 ppm and 40 ppm can cause electrolytes imbalance and dyslipidemia in hepatic, renal, brain and cardiac tissues of male albino rats.

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