Up-regulation of adiponectin, its isoforms and receptors in end-stage kidney disease

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Abstract

Background. Despite the favourable effects of adiponectin on the vasculature and insulin resistance (IR), levels are increased in patients with end-stage kidney disease (ESKD), in whom both IR and atherosclerosis are prevalent.

Methods. To investigate this paradox, we examined the distribution of adiponectin isoforms, the expression of adiponectin receptor (AdipoR) mRNA on peripheral blood mononuclear cells (PBMC) in 41 patients with ESKD on haemodialysis and 41 matched controls, and its function by adenosine monophosphate-activated protein kinase (AMPK) phosphorylation of AdipoR on PBMC. We also compared the expression of AdipoR on PBMC with that on muscle and subcutaneous and visceral fat in 10 patients undergoing elective cholecystectomy.

Results. The proportion of the high molecular weight (HMW) isoform of adiponectin was increased in the dialysis group ($P = 0.001$), even though these patients were significantly insulin resistant compared with controls ($P = 0.006$). AdipoR1 and AdipoR2 on PBMC were also increased in patients with ESKD ($P < 0.05$ and $P = 0.007$, respectively), but levels did not correlate with IR, the HMW isoform or other anthropometric measurements. There was a strong correlation between AdipoR1 and AdipoR2 on PBMC in ESKD and in subcutaneous and visceral fat in 10 patients undergoing elective cholecystectomy.

Conclusions. IR in ESKD is not explained by the change in isoformic distribution, or by AdipoR down-regulation or dysfunction. Rather, this receptor-ligand axis is up-regulated and may be a beneficial response to the inflammatory milieu of ESKD.

Keywords: adiponectin; adiponectin receptors; chronic kidney failure; dialysis; inflammation; insulin sensitivity; metabolic syndrome; uraemia

Introduction

End-stage kidney disease (ESKD) is associated with multiple risk factors for premature vascular disease. These include a high incidence of insulin resistance (IR) and other features of the metabolic syndrome. Adiponectin is produced almost exclusively by adipose tissue and appears to have anti-inflammatory, anti-atherogenic and insulin-sensitizing properties [1]. Paradoxically, adiponectin levels are increased in patients with kidney failure [2], despite their propensity to IR and vascular disease, but are decreased in obesity, type 2 diabetes and coronary artery disease [1]. Observations in experimental animals demonstrate improved insulin sensitivity with adiponectin administration and protection from atherosclerosis in Apo-E deficient mice [1].
Little has been reported on the expression of AdipoRs in various disease states in humans. It remains unexplained as to why adiponectin is elevated in patients with ESKD [2], given that this group is susceptible to IR and vascular disease. It is possible that low levels of the HMW isofrom are masked by an overall increase in adiponectin concentration. Alternatively, the expression of AdipoR may be down-regulated in this population, thus affecting adiponectin/receptor signalling or AdipoR function may itself be impaired in ESKD. To examine these possibilities, we investigated in 41 patients with ESKD and 41 matched controls; (i) the concentration of the native molecule and the distribution of its isofroms; (ii) the level of AdipoR mRNA on peripheral blood mononuclear cells (PBMC); and (iii) the ability of adiponectin to signal via these receptors. We also investigated whether AdipoR mRNA on PBMC in healthy subjects were present in physiologically significant quantities comparable with those on muscle and subcutaneous and visceral fat.

**Subjects and methods**

**Patients and controls**

Forty-one subjects (20 males; 21 females; age 18–79 years) (Table 1) were recruited from the Prince of Wales and St George Hospital haemodialysis units, Sydney, Australia. The causes of end-stage renal disease were follows: ischaemic hypertensive nephrosclerosis (n = 7), chronic glomerulonephritis (GN), i.e. without renal biopsy, (n = 6), mesangial IgA GN (n = 4), reflux nephropathy (n = 4), focal and segmental glomerulosclerosis (n = 3), polycystic kidney disease (n = 2), analgesic nephropathy (n = 2) and one each of the following: medullary cystic kidney disease, Wegeners GN, immunotactoid GN, lupus nephritis, lithium nephrotoxicity, mesangiocapillary GN, thrombotic thrombocytopenic purpura-haemolytic uraemic syndrome (TTP-HUS) and bilateral nephrectomy for renal carcinoma. In five cases, the cause was unknown. The duration of haemodialysis ranged from 1 to 12 years, with an average of 3.5 years. Patients were free of clinically overt infection and those with lupus, Wegeners GN and TTP-HUS did not have active disease and were not being treated with immunosuppression at the time of recruitment. Patients received 12–15 h of haemodialysis per week using bicarbonate dialysate. Patients with diabetes were excluded because of the known effect of (type 2) diabetes on plasma adiponectin levels [1].

In some analyses, patients were stratified in terms of whether they were being treated with angiotensin-converting enzyme inhibitors (ACEI) or angiotensin II receptor antagonists (AIIRA). ACEI and AIIRA were included as a single group, as current evidence suggests that there is no difference in their effect on total adiponectin levels [7]. A detailed medical history and clinical assessment was performed to assess the presence of coronary artery, cerebrovascular and peripheral vascular disease. Control subjects (n = 41; 22 males; 19 females; aged 25–71 years) consisted of healthy volunteers without clinical or laboratory evidence of renal disease or diabetes. All procedures were approved by the Prince of Wales and St George Hospitals’ Human Research Ethics Committees, and all subjects gave written informed consent.

**Blood samples**

After an overnight fast, venous blood was taken for measurement of a full blood count, plasma lipids [cholesterol, triglycerides, high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol], creatinine, glucose, insulin, plasma adiponectin and high sensitivity C-reactive protein (hs-CRP). Samples were chilled immediately, centrifuged at 3000rpm and the plasma analysed immediately or kept at −20°C until analyses were performed. Adiponectin was measured using an enzyme-linked immunosorbent assay (R&D, Minneapolis, USA). The hs-CRP was measured by nephelometer. Other tests were performed in a routine laboratory. IR was estimated using the Homoeostasis Model Assessment index (HOMA-R) i.e. [plasma glucose level (mmol/l) × plasma insulin (µU/ml)]/22.5] which has been validated for use in this population.

**Anthropometry**

Anthropometric data were obtained for each subject at enrolment into the study. They included weight in kilograms (dry weight for those on haemodialysis) and height in centimetres. Body mass index (BMI) was calculated by weight (kg)/height (m)² and waist to hip ratio (WHR).

**Adiponectin receptors on PBMC**

To explore the relationship between adiponectin and its receptors, the expression of AdipoR1 and AdipoR2 on PBMC was investigated. Ten millilitres of blood were collected into ethylenediaminetetraacetic acid (EDTA) and centrifuged at 3000 rpm for 10 min. White cells from the buffy coat were purified by differential lysis of erythrocytes using a buffer containing 155 mM ammonium chloride, 10 mM sodium bicarbonate and 0.1 mM EDTA. Total cellular RNA was extracted using Trizol (Life Technologies, France). For quantitative polymerase chain reaction (PCR), total RNA was reverse transcribed using random hexameric primers and...
RevertAid reverse transcriptase (Fermentas, Life Sciences, Ontario, Canada). The cDNA was quantified by real-time PCR on a Rotor-Gene 3000 (Corbett Research, Sydney, Australia), using primers specific for human AdipoR1: forward 5'-CTT CTA GTC CTC CAC CCA GC-3', and reverse 5'-GAC AAA GCC CTC AGC GAT AG-3', human AdipoR2: forward 5'-GAC ATG TCC CTC TCG CA-3' and reverse 5'-TGG TGC CAA ATG TTG CCT GT-3', and standardized to 18S RNA using specific primers (Quantum RNA, Ambion, Adelaide, Australia). PCR amplification was performed in a volume of 25 µl containing 0.4 mM of each primer, 5.0 mM MgCl2, 2.0 mM dNTP, and 0.02 units/ml DNA polymerase (Bioline, Sydney, Australia), using primers specific for human AdipoR1:

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forward 5'-GAC AAA GCC CTC AGC GAT AG-3'
reverse 5'-TGG TGC CAA ATG TTG CCT GT-3'
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and specific signal and amplification of specific transcripts was confirmed by melting curve profiles at the end of each PCR. The PCR products were also separated by electrophoresis on 1.5% agarose gels and evaluated for specificity by ethidium bromide staining under UV light.

**Tissue samples**

To further examine the physiological significance of mRNA for AdipoR1 and AdipoR2 on PBMC, we compared these mRNA levels with those in skeletal muscle and subcutaneous and visceral fat. Samples were obtained from otherwise healthy patients undergoing elective cholecystectomy and PBMC were collected simultaneously. There were seven males and three females, aged 45–78 years (Table 2). None had evidence of diabetes or renal disease and were clinically well at the time of surgery. Fresh tissue samples were dissected to avoid visible vessels and washed thoroughly with sterile saline. They were then placed into RNA Later (Ambion) for 24 h at room temperature and stored at −80°C until RNA extraction. RNA extraction, PCR amplification and cDNA for AdipoR1 and AdipoR2 were quantified by real-time PCR as described before.

**Superose column chromatography**

To quantify the relative amounts of each isoform, adiponectin in plasma was resolved into molecular weight, medium molecular weight and high molecular weight isoforms by chromatography on a fast protein liquid chromatography (FPLC) apparatus as previously described [8].

**Stimulation of PBMC with adiponectin**

We examined the phosphorylation of AMPK in response to adiponectin to confirm the signalling capacity of AdipoR on PBMC. Whole blood in EDTA was obtained from 10 of the control subjects and 10 with ESKD, chosen at random. After a 1:1 dilution with a balanced salt solution, Ficoll-Paque PLUS (Amersham Biosciences, Uppsala, Sweden) density gradient centrifugation (3000 g, 30 min, 20°C) was used to isolate PBMC. Cells harvested from the interphase were washed twice in a balanced salt solution and resuspended in RPMI-1640. Cell viability, as determined by trypan blue exclusion, was >95% in all experiments. Cells were cultured in RPMI-1640 medium supplemented with penicillin G (100 U/ml), streptomycin (100 µg/ml), t-glutamine (2 mM) and 5% foetal calf serum (Life Technologies, New York, USA). Cells were serum-starved for 16 h before use. Recombinant adiponectin (R & D Systems, Minneapolis, USA) (<1.0 EU/µg lipopolysaccharide) was then added at a concentration of 1 µg/ml for 0–15 min. The recombinant adiponectin was analysed by FPLC [8] and found to consist primarily of the HMW isoform. The cells were rapidly washed with ice cold phosphate-buffered saline and heated to 95°C for 5 min in reducing sodium dodecyl sulphate (SDS) sample buffer containing 1 mM sodium orthovanadate (Sigma Chemical, St Louis, USA) and 1 mM sodium fluoride (Ajax Chemicals, Sydney, Australia). Proteins were resolved by SDS-PAGE on 11% acrylamide gels and transferred to nitrocellulose membranes. A polyclonal anti-rabbit antibody against phospho-(Thr172)-AMPK (Upstate, Lake Placid, NY, USA) was applied at a concentration of 1:2000 overnight, then detected by a horseradish peroxidase conjugated anti-rabbit antibody (Bio-Rad Laboratories, Richmond, CA, USA) and enhanced chemiluminescence (Pierce, Rockford, IL, USA). The signals on film were analysed with Discovery Series Quantity One 1-D Analysis Software (Bio-Rad Laboratories).

**Statistical analysis**

All statistical analyses were performed using the Statistical Package for Social Science (SPSS 13.0, SPSS Inc. Chicago, IL, USA). The data are shown as the mean ± SD or SEM. Statistical significance was assessed using paired and unpaired Student’s t-tests or the Mann-Whitney U-test. Differences between groups for plasma adiponectin, HOMA-R and HMW isoforms of adiponectin were also compared after adjustment for age by General Linear Modelling function analysis. As the population data for plasma adiponectin, HOMA-R, hs-CRP, triglycerides, total cholesterol, LDL, HDL, AdipoR1, AdipoR2, HMW adiponectin, age, BMI and WHR were not normally

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**Table 2. Subjects undergoing elective cholecystectomy—clinical and laboratory data**

<table>
<thead>
<tr>
<th></th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number</strong></td>
<td>10</td>
</tr>
<tr>
<td><strong>Males</strong></td>
<td>7</td>
</tr>
<tr>
<td><strong>Age (year)</strong></td>
<td>58 ± 10</td>
</tr>
<tr>
<td><strong>BMI</strong></td>
<td>27.6 ± 5.7</td>
</tr>
<tr>
<td><strong>HOMA-R</strong></td>
<td>3.0 ± 2.4</td>
</tr>
<tr>
<td><strong>hs-CRP (mg/l)</strong></td>
<td>2.0 (1.0–13.0)</td>
</tr>
<tr>
<td><strong>Total Cholesterol (mmol/l)</strong></td>
<td>4.8 ± 1.5</td>
</tr>
<tr>
<td><strong>Triglycerides (mmol/l)</strong></td>
<td>1.7 ± 1.3</td>
</tr>
<tr>
<td><strong>HDL cholesterol (mmol/l)</strong></td>
<td>1.2 ± 0.4</td>
</tr>
<tr>
<td><strong>LDL cholesterol (mmol/l)</strong></td>
<td>2.9 ± 1.2</td>
</tr>
<tr>
<td><strong>Plasma adiponectin (µg/ml)</strong></td>
<td>5.8 ± 2.4</td>
</tr>
<tr>
<td><strong>HMW adiponectin proportion</strong></td>
<td>0.26 ± 0.03</td>
</tr>
<tr>
<td><strong>HMW adiponectin (µg/ml)</strong></td>
<td>1.5 ± 0.6</td>
</tr>
</tbody>
</table>

NS, not significant. Values are expressed as mean ± SD. hs-CRP data are expressed as median (range).
distributed, log-transformed values were used for statistical analysis. Correlations between adiponectin and all other parameters were examined by simple logistic regression analysis. Pearson correlation analysis was used to evaluate the relationship between individual variables and plasma adiponectin. \( P < 0.05 \) was considered statistically significant.

**Results**

**Subject characteristics**

Anthropometric and biochemical data for patients and controls are shown in Table 1. There were no significant differences for BMI and WHR between the groups, although there was a significant difference in age. The ESKD group was insulin resistant compared with the controls (\( P = 0.006 \)). Although the patient group had a lower LDL cholesterol, this probably reflected treatment with a statin (\( n = 14 \) in ESKD group vs \( n = 4 \) in controls). However, despite this treatment, ESKD patients demonstrated relative hypertriglyceridaemia compared with the control group (\( P < 0.05 \)). CRP was also increased in those with ESKD (\( P < 0.0005 \)). Twelve in the ESKD group and two in the control group had a history of vascular disease.

**Plasma adiponectin, HMW proportion and HMW total**

Plasma adiponectin levels were significantly higher in the ESKD group (Figure 1A). This group also had a significantly higher proportion of the HMW isoform (Figure 1B) (1.2 \times control values) and an increased concentration of HMW adiponectin (Figure 1C) (2.6 \times control values). Although patients with ESKD were older in comparison with controls (Table 1), a two-way analysis of variance showed that there was no additional influence of age on the level of adiponectin or its HMW isoform (\( P = 0.22 \) and \( P = 0.29 \), respectively). The expected sexual dimorphism of adiponectin in ESKD was seen, with higher levels of total and HMW adiponectin (\( P = 0.002 \) and \( P = 0.003 \), respectively) in females. Total adiponectin levels were inversely correlated with HOMA-R in those with ESKD (\( R = -0.50, P = 0.003 \)), as were the absolute amount and proportion of the HMW isoform (\( R = -0.56, P = 0.001 \) and \( R = -0.50, P = 0.003 \), respectively). However, there was no correlation between HOMA-R and the proportion of HMW adiponectin in control subjects. There was a significant correlation between the absolute amount of the HMW isoform and HDL cholesterol in both controls and ESKD (\( R = 0.39, P = 0.01 \) and \( R = 0.39, P = 0.02 \), respectively). Adiponectin levels correlated inversely with BMI and WHR in ESKD (\( R = -0.41, P = 0.007 \) and \( R = -0.46, P = 0.003 \)) and WHR in controls (\( R = -0.58, P < 0.0005 \)). There was no significant correlation with CRP in either group. There was no difference in levels or in the multimeric distribution of adiponectin between those who did or did not have vascular disease.

**Adiponectin receptors in PBMC**

Levels of AdipoR1 and AdipoR2 mRNA on PBMC were significantly increased in patients with ESKD (Figure 2), but there was no significant difference in receptor levels between males and females from the control or ESKD groups. Levels of AdipoR1 and AdipoR2 on PBMC were not related to anthropometric measurements, HOMA-R, total adiponectin or multimeric distribution in either group. However, there was a strong correlation between levels of AdipoR1 and AdipoR2 on PBMC in those with ESKD (Figure 3). This relationship was not seen in controls. There were increased amounts of AdipoR1 compared with AdipoR2 in both groups (Figure 2). There was no difference in AdipoR levels between those who did or did not have vascular disease.

**Effect of ACEI/AIIRA and statins on adiponectin and its receptors**

Of the 41 ESKD patients, 13 were on ACEI or AIIRA. Non-parametric analysis showed no difference in levels of total plasma adiponectin, the absolute amount of HMW isoform, the proportion of HMW isoform, or mRNA for AdipoR1 and AdipoR2 between...
those taking and those not taking an ACEI or AIIRA. Patients receiving a statin (n = 14) had significantly lower LDL-cholesterol (P = 0.02) and increased mRNA for AdipoR1 (P = 0.02) compared with untreated patients, but there was no difference in total adiponectin or the HMW isoform.

**AdipoR in fat, muscle and PBMC in subjects undergoing cholecystectomy**

Apart from a significant increase in AdipoR1 in PBMC when compared with subcutaneous fat, there was no significant difference in mRNA expression of AdipoR1 and AdipoR2 when compared across the different tissues (Figure 4). Levels of mRNA for AdipoR1 and AdipoR2 in PBMC were similar to and correlated with those on subcutaneous fat (R = 0.76, P < 0.05 and R = 0.78, P < 0.05, respectively). As with PBMC, there was a strong correlation between levels of mRNA for AdipoR1 and AdipoR2 in subcutaneous and visceral fat (R = 0.95, P < 0.0005 and R = 0.67, P < 0.05, respectively); this relationship was not seen in skeletal muscle.

**Adiponectin induces activation of AMPK in PBMC**

Exposure of PBMC to recombinant adiponectin led to a comparable increase in AMPK phosphorylation at 5 min in both control and ESKD groups (Figure 5A and B). By 15 min, AMPK phosphorylation had decreased essentially to background levels.

**Discussion**

This study shows that in patients with ESKD there is an increase in HMW adiponectin in the presence of elevated levels of mRNA for AdipoR1.
and AdipoR2 on PBMC. Moreover, the function of AdipoR on PBMC, as measured by the downstream phosphorylation of AMPK, was equivalent in controls and subjects with ESKD. We also confirmed that AdipoR mRNA on PBMC in healthy subjects were present in physiologically significant quantities comparable with those on muscle and subcutaneous and visceral fat.

Relatively low serum adiponectin predicts cardiovascular events in ESKD [2] and correlates with cardiovascular risk factors such as hypertriglyceridaemia, low HDL cholesterol and raised CRP [9]. Our finding of an increased proportion of the HMW moiety in ESKD was unexpected, since these subjects had a significantly raised HOMA-R and this isoform correlates with insulin sensitivity [3]. As well, mutant forms of adiponectin, which are unable to polymerize into HMW species, are linked with diabetes [1]. Hence, IR associated with ESKD is not explained by a low percentage or concentration of the HMW isoform. Nevertheless, both the total and proportion of HMW adiponectin correlated negatively with HOMA-R and positively with metabolically favourable parameters such as low BMI, WHR and an increased HDL fraction.

Our subjects with ESKD were carefully matched for body characteristics with controls to ensure the reliability of the data obtained. However, several of those on dialysis were receiving ACEI, AIIRA and statins, and our controls were significantly younger in comparison with ESKD subjects. While ACEI and AIIRA have been reported to increase adiponectin levels [10], there was no significant difference in AdipoR, total adiponectin or the proportion of HMW isoform between treated and untreated patients. Hence, the differences between controls and dialysis patients are likely to be a result of ESKD and/or the process of haemodialysis rather than an effect of medication. We also found no difference in adiponectin levels or the HMW proportion in patients on statins compared with other subjects with ESKD, which concurs with other studies [11]. Some studies have found an independent effect of age on adiponectin levels [12]. Our subjects were carefully matched for anthropometric characteristics; controls were on average 9 years younger than patients. However, statistical analysis showed that this difference did not have an additional impact on adiponectin levels or its multimeric distribution.

Subjects with hypertension and endothelial dysfunction without kidney impairment have been documented to have low adiponectin levels [13]. Patients on haemodialysis are often hypertensive secondary to fluid overload and/or endothelial dysfunction and 13 of our patients were receiving ACEI and AIIRA. Despite the potential for hypertension in ESKD, we found elevated levels of adiponectin and its HMW isoform in this group. Whether hypertension per se limits the increase in adiponectin levels or AdipoR in patients with ESKD remains unresolved.

Adiponectin is involved in glucose utilization in skeletal muscle, but we did not see any relationship between plasma adiponectin levels and AdipoR1 or AdipoR2 expression in muscle or PBMC. The interaction of adiponectin with its receptor is not well understood, but AdipoR may not display the inverse ligand-receptor relationship observed, for example,
Adiponectin, its isoforms and receptors in ESKD

with insulin and its receptor. Thus, if the concentration of adiponectin was the crucial determinate of receptor interaction, then the quantities of each of the adiponectin multimers we have described would be sufficient to signal continuously via these receptors given their reported binding affinities. Furthermore, adiponectin may exert anti-inflammatory potential at a pre-receptor level. It binds directly to platelet-derived growth factor-BB [14] and lipopolysaccharide [15], thus controlling their bioavailability.

Specific receptors have been described for the various forms of adiponectin [5]. In mice, levels of AdipoR1 are greater than those of AdipoR2 in skeletal muscle and levels of both are greater than in PBMC [5]. In contrast, we found that levels of AdipoR1 and AdipoR2 mRNA in PBMC in normal subjects were similar to those in subcutaneous and visceral fat and in skeletal muscle, demonstrating their presence in physiological quantities in PBMC. A previous report of receptor levels in PBMC in healthy subjects found increased amounts of AdipoR1 compared with AdipoR2 [16], a finding that concurs with our data in controls and ESKD.

The clinical significance and the factors controlling the expression of these receptors are not clear. In some, but not all studies, polymorphisms in either AdipoR1 and/or AdipoR2 have been associated with type 2 diabetes and IR [17]. AdipoR levels in muscle do not change acutely after exercise [18] or insulin infusion [19] but, in type 2 diabetes, therapy with rosiglitazone induces down-regulation of AdipoR1 in muscle and up-regulation in adipose tissue [6]. Levels of AdipoR2 did not change in either tissue. Most studies of AdipoR in monocyte/macrophages have shown an anti-inflammatory role for these cells on the addition of adiponectin [20]. Haemodialysis induces a pro-inflammatory state [21] and we found AdipoR correlated strongly with AdipoR2 in ESKD, but not in controls. Our data also confirmed that AdipoR on PBMC in ESKD are functional, as intracellular signalling via AMPK phosphorylation was induced by incubation with adiponectin to a degree comparable with that in PBMC from controls. These results suggest that increases in AdipoR on PBMC may be an appropriate anti-inflammatory response to the uraemic milieu and that both receptors may respond to a stimulus specific to ESKD. Hence, it may be beneficial clinically to further increase levels of adiponectin and its receptors in ESKD via medication or weight loss [22]. Thiazolidinediones, for example, increase levels of adiponectin [22] and its HMW isoform [3]. Their longitudinal effects on the metabolic state of ESKD may prove to be of clinical significance.

Conclusion

We conclude that the paradox of high adiponectin levels in ESKD, in the face of IR and atherosclerosis, is not explained by decreased levels of HMW adiponectin nor by receptor dysfunction-expression. Rather, the adiponectin/receptor system appears to be up-regulated in ESKD possibly as an appropriate counter-regulatory response to the uraemic milieu.

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Conflict of interest statement. None declared.

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