A Comparison of the Effects of 5- and 6-Hydroxydopamine on the Isolated Canine Saphenous Vein

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SUMMARY We studied and compared the effects of 5- and 6-hydroxydopamine (5- or 6-OHDA) on venous tone and on adrenergic and nonadrenergic responses of the isolated canine saphenous vein. In the tissue bath, both 5- and 6-OHDA caused increases in tone and abolished adrenergic responses to transmural nerve stimulation. Effects of 6-OHDA were blocked by desmethylimipramine. 6-OHDA reduced norepinephrine levels of venous strips to 15% of those in control strips. Neither 5- nor 6-OHDA markedly altered peak contractile responses to norepinephrine but 6-OHDA prolonged the response to norepinephrine. Both compounds reduced responses to tyramine, with 6-OHDA producing a greater reduction than 5-OHDA. Large contractile responses to 5-OHDA were blocked only partially by treatment of strips with 6-OHDA, suggesting that contractile responses to 5-OHDA were mediated by direct and indirect actions. These results suggest differences in the actions of 5- and 6-OHDA on adrenergic terminals and smooth muscle in saphenous veins. The results of the experiments suggest that both 5- and 6-OHDA may be useful pharmacological interventions for the study of adrenergic mechanisms in isolated blood vessels.

ADRENERGIC mechanisms in isolated, denervated canine saphenous veins have been studied following reserpine pretreatment and following surgical denervation. Each of these techniques produced functional and/or biochemical destruction of adrenergic terminals. However, reserpine has multiple pharmacological effects which make interpretation of such experiments difficult. Unilateral surgical sympathectomy permits the study of innervated and denervated veins from the same animal. However, nonadrenergic pathways, if present, also may be disrupted during the surgical procedures.

Selective chemical sympathectomy with 6-hydroxydopamine (6-OHDA) has been used to study adrenergic mechanisms in the peripheral and central nervous system. Cardiovascular effects of this catecholamine analogue have been studied in intact dogs and frogs and in isolated hearts and arteries prepared from cats, rats, rabbits, and guinea pigs which had previously been treated with 6-OHDA. These earlier investigations showed that 6-OHDA elicited an initial sympathomimetic effect that was followed by adrenergic neuronal blockade and prejunctional and/or postjunctional supersensitivity to exogenously administered norepinephrine. Biochemical depletion of norepinephrine also was demonstrated.

The influence of 6-OHDA on adrenergic mechanisms in veins has not been widely studied. In one study, 6-OHDA was applied in vitro to rat portal veins. These investigators were able to define partially the in vitro pharmacology of 6-OHDA and to demonstrate features of catecholamine inactivation in this vein. 5-Hydroxydopamine (5-OHDA) is a second isomer of norepinephrine which has not been studied extensively. We, therefore, sought to define further the in vitro pharmacology of 5-OHDA and to compare the effects of 5-OHDA and 6-OHDA.

The in vitro effects of 5- and 6-OHDA were studied in isolated canine saphenous veins. Responses to transmural electrical stimulation, tyramine, norepinephrine, and acetylcholine were compared before and after treatment with 5- or 6-OHDA in order to determine the influence of such treatments on neurogenically mediated transmitter release, nonneurogenically mediated transmitter release, alpha receptor-mediated smooth muscle responses, and nonadrenergic smooth muscle responses, respectively.

Methods

Mongrel dogs of either sex (12–20 kg) were anesthetized with pentobarbital (25 mg/kg, iv). Both lateral saphenous veins were excised and cut into helical strips (2.0 X 0.3 cm). These freshly prepared strips were suspended in tissue baths in a physiological salt solution (PSS) of the following composition (mM): NaCl (127), KCl (2.7), CaCl₂ (1.8), MgCl₂ (0.5), glucose (11), Tris (23.8). The pH was adjusted to 7.4 with 6 N HCl. During experiments, the temperature of the PSS was maintained at 37 ± 1°C and the PSS was gassed continuously with 100% O₂.
A modification of the technique of Vanhoutte et al. was used to study neurogenic adrenergic venoconstrictor responses. Strips were suspended in 50-ml baths (Metro Scientific) between a specially designed tissue holder and a Grass FT.03 C force transducer. The tissue holder consisted of a Plexiglas rod with hooks and vertically directed parallel platinum wires which were connected to a stimulator (Grass, or E & M Instrument Co.). Monopolar rectangular pulses, 5-msec duration 125 V, were applied through the PSS at various frequencies.

Strips initially were suspended between the parallel platinum wires at a load of 2 g and allowed to rest undisturbed for 20 minutes. Following this equilibration period, each strip was placed at the optimal point of its length-tension curve. At this time a reference cumulative concentration-response curve (CRC) for norepinephrine (10⁻⁵, 10⁻⁴, 10⁻³, 10⁻² M) was determined. Strips then were allowed to reach a stable baseline in drug-free PSS and at the same time were stimulated for 1-minute periods at a frequency of 2 Hz. Responses to 2 Hz were obtained at 5-minute intervals until reproducible responses were present (usually 2-2.5 hours after preparation of strips). Delivery of the stimuli at regular intervals was accomplished by connecting the stimulating electrodes through a bank of rotating switches (Zenith) which had a cycle length of 6 minutes. Switches were connected in series between stimulators and electrodes. The switch-closed position was adjusted to provide a 1-minute stimulus period with a 5-minute stimulus-free period during each 6-minute cycle.

Five- or 6-OHDA (Regis Chemical Co.) was prepared fresh, daily, in PSS at a concentration of 10⁻⁴ M. This resulted in a colored solution (orange for 6-OHDA and yellow for 5-OHDA) which has been suggested to reflect spontaneous oxidation at physiological pH. Solutions of other pharmacological substances also were prepared fresh, daily, in PSS.

The following experiments were performed:

Effects of 5- and 6-OHDA on Venomotor Tone, Responses to Transmural Stimulation and Norepinephrine

Five- or 6-OHDA (10⁻⁴ M) was added to the bath during the period of repeated stimulation at a frequency of 2 Hz and was allowed to remain in the bath for a period of 90-120 minutes. At that time, the bathing medium was replaced by drug-free PSS and the stimulators were turned off. During the treatment period, the bathing medium was drained at 20 to 30-minute intervals and replaced with PSS containing fresh 5- or 6-OHDA. This was done to wash away spontaneous oxidation products of 5- or 6-OHDA (the discoloration of the bathing medium increased with time) and to maintain a relatively constant concentration of drug in the bath. After re-immersion in drug-free PSS, strips were washed repeatedly at 15- to 30-minute intervals until a stable baseline level of tone had been achieved. At that time, responses to transmural stimulation were tested.

The influence of desmethylimipramine (DMI) (Norpramin, Lakeside) on the responses to 6-OHDA also was determined. This compound inhibits the active uptake of catecholamines and related compounds into adrenergic terminals and blocks the in vivo effects of 6-OHDA. In these experiments, DMI (3 x 10⁻⁶ M) was added to the bath 10 minutes prior to the addition of 6-OHDA. DMI remained in the bathing medium during the entire period of exposure to 6-OHDA.

In several experiments we also determined the influence of time, 6-OHDA, and 6-OHDA in the presence of DMI on norepinephrine levels in the venous strips. Strips were treated as above and, after a final test of responses to transmural stimulation, blotted dry and rapidly frozen on dry ice. Strips were stored individually at −48°C and assayed individually for norepinephrine by a previously described method. The frozen strips were homogenized by hand and sonicated in iced acidified butanol. The homogenate was extracted with phosphate buffer (0.1 M, pH 6.5). Samples of this extract were reacted with iodine to convert norepinephrine to its trihydroxyindole derivative. Samples were read in an Aminco-Bowman spectrofluorometer at 385/485 nm (activation/emission), and norepinephrine levels were determined from the linear portion of an appropriate standard curve, determined simultaneously. Recoveries were approximately 85%, and a nonparametric (Mann-Whitney U) test was used to compare norepinephrine levels in the saphenous vein in these three experimental groups.

Influence of 5- and 6-OHDA on Venoconstrictor Responses to Norepinephrine, Tyramine, and Acetylcholine

In three groups of strips, CRCs for acetylcholine (10⁻⁶, 10⁻⁵, 10⁻⁴ M), tyramine (10⁻⁷, 10⁻⁶, 10⁻⁵, 10⁻⁴ M), and norepinephrine (10⁻⁶, 10⁻⁵, 10⁻⁴ M), respectively, were determined with a 20- to 30-minute interval between exposure to different agonists. Then, one group of strips was treated with 5-OHDA and another was treated with 6-OHDA (as above) for 80-120 minutes. The third group of strips was not treated with either 5- or 6-OHDA and, therefore, served as a time control. At the conclusion of the 80- to 120-minute interval, strips were allowed to return to a baseline level of tone and responses to tyramine, norepinephrine, and acetylcholine were reevaluated, in sequence. For each group of strips, peak responses to each concentration of agonists before and after the treatment period were compared by paired t-test. A P value less than
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0.05 was the criterion for statistical significance. Each strip was used as its own control, and the time control served to determine effects of time and to control for the nonrandom sequence of drug administration. For each agent tested, only a partial CRC (i.e., without maximal responses) was determined. Submaximal concentrations of these agents (particularly norepinephrine) were used to avoid prolonged washout periods between dose-response curves, tachyphylaxis to these agents, and permanent changes in responsiveness and baseline tone which follow exposure to maximal concentration of norepinephrine (M. R. Goldberg, unpublished observations).

Results

Responses to Trasmural Electrical Stimulation

The response of saphenous vein strips to transmural stimulation was dependent on stimulus frequency (Fig. 1). These responses were inhibited by phentolamine (10^{-8} M) and bretylium (2.5 × 10^{-6} M) as previously described.

Influence of 5- and 6-OHDA on Venomotor Tone and Contractile Responses to Transmural Stimulation

Strips in one group were stimulated repeatedly at a frequency of 2 Hz and served as a time control. In this group, no consistent changes in responses to transmural stimulation, baseline venous tone, or responses to norepinephrine were noted. When added to the perfusate, 6-OHDA (10^{-4} M) elicited a transient contraction equal to 20 ± 3% (SEM) of the response to norepinephrine (10^{-6} M) (Fig. 2, top trace). This transient contraction was followed by a more gradual increase in tone which was well maintained. Replacing the perfusate with solution containing fresh 6-OHDA was followed by a transient decrease in tone. Subsequently, the gradual increase in tone was resumed. After 60-90 minutes, the level of tone reached a plateau and began to decline, after replacing the perfusate with solution containing fresh 6-OHDA. At that time, strips were washed. Over the next 60-90 minutes, tone returned to a baseline level similar to that observed prior to treatment.

![Figure 1](https://example.com/figure1.png)  
**Figure 1** Records from experiments illustrating the effects of phentolamine and bretylium on responses of saphenous vein to transmural nerve stimulation and to norepinephrine. Norepinephrine was used in concentrations of 10^{-9}, 10^{-8}, 10^{-7}, and 10^{-6} M, added in cumulative fashion.
In 7 of 17 strips after addition of 6-OHDA, the initial response to the 2-Hz stimulus was increased relative to the responses prior to treatment. However, for all strips, the difference between this response and the response prior to addition of 6-OHDA was not significant. After the addition of 6-OHDA to the bath, as basal tone increased the rate of rise and amplitude of responses to 2 Hz diminished. When the increase in baseline tone reached a steady level, responses to electrical stimulation were no longer observed, or were marked only by a transient relaxation at the end of the stimulus period. After reequilibration in drug-free PSS, strips were not responsive to transmural stimulation at any frequency (Fig. 2, top trace).

When added to the venous strips, 5-OHDA (10^-4 M) elicited a large, rapidly developing contraction equal to 111 ± 6% the response to norepinephrine (10^-6 M) (Fig. 2, bottom trace). This contraction peaked and then the strip relaxed spontaneously to a steady contracture. The original 5-OHDA was replaced with fresh 5-OHDA at 20- to 30-minute intervals. Each addition of fresh 5-OHDA elicited a contraction which peaked at a level below that elicited by prior additions of 5-OHDA. However, the steady increased tone which followed each renewal of 5-OHDA was maintained at a level higher than the preceding one (Fig. 2, bottom trace). As the level of the tone established after each peak contraction increased, the responses to transmural stimulation at 2 Hz were progressively attenuated. Sixty minutes after washout, the level of baseline tone was not different from the initial level, and responses to transmural stimulation were abolished.

DMI (3 × 10^-6 M) inhibited responses to transmural stimulation by 34 ± 1%. Under these conditions, 6-OHDA (10^-4 M) still elicited a small initial contraction equal to 7 ± 1% of the response to norepinephrine (10^-6 M). The increase in basal tone which followed the addition of 6-OHDA to the bath was abolished by prior treatment with DMI.

In the presence of DMI, 6-OHDA reduced responses to transmural stimulation to 9 ± 4% the response obtained prior to addition of 6-OHDA. During this period of combined exposure to 6-OHDA and DMI, responses to electrical stimuli progressively diminished and occasionally were abolished. After removal of both agents from the bath, responses to electrical stimuli again could be obtained, although they were equal to only 27 ± 7% of the response prior to treatment with either agent.

Norepinephrine content of venous strips was determined for a series of strips treated as time controls, or with 6-OHDA, or 6-OHDA + DMI. Strips were assayed individually for total norepinephrine content (μg) and norepinephrine concentrations (μg/g) were determined. Norepinephrine levels (mean ± SEM) were 1.27 ± 0.22 μg/g, 0.19 ± 0.08 μg/g, and 1.62 ± 0.65 μg/g, for strips treated as control, with 6-OHDA, and with 6-OHDA and DMI.
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Influence of 5- and 6-OHDA on Contractile Responses to Norepinephrine, Tyramine, and Acetylcholine

Partial CRCs for acetylcholine (10^{-6} to 10^{-4} M), tyramine (10^{-7} to 10^{-4} M), and norepinephrine (10^{-8} to 10^{-6} M) were determined for control strips and strips treated with 5- or 6-OHDA. Responses to these agents before and after a treatment period were compared (Figs. 3-5).

In time control strips, responses to norepinephrine were identical before and after the treatment period. In 5- or 6-OHDA-treated strips, responses to norepinephrine were depressed after treatment (Figs. 2 and 3). These differences were small, but were statistically significant for all concentrations of norepinephrine in strips treated with 5-OHDA and the lowest concentration of norepinephrine for strips treated with 6-OHDA.

A comparison also was made of the half relaxation time (T_{1/2}) following the treatment period in strips treated as time control or with 5- or 6-OHDA. T_{1/2} was defined as the time (minutes) required following immersion in drug-free PSS for the norepinephrine-induced contraction to relax to a level of one-half the total force generated in the presence of norepinephrine (10^{-6} M) (Fig. 2, right side). At the concentrations employed in this study, this parameter reflects the ability of strips bathed in PSS to dispose of exogenous norepinephrine, presumably through neuronal uptake. As seen in Figure 2, after treatment with 6-OHDA, the initial relaxation following removal of norepinephrine from the bath is delayed relative to that in the control strip. Approximate T_{1/2} values (mean ± SEM) were 1.27 ± 0.19, 2.97 ± 0.36, and 1.68 ± 0.15 for control, 6-OHDA-, and 5-OHDA-treated strips, respectively. T_{1/2} was significantly increased in 6-OHDA-treated strips. The degree of prolongation of the T_{1/2} induced by 6-OHDA was similar to that induced by treatments known to inhibit neuronal uptake in saphenous vein, i.e., surgical denervation and cocaine. Thus, T_{1/2} was 134% of control for 6-OHDA-treated strips, 137% of control for surgically denervated strips, and 124% of control for cocaine-treated strips (data for surgical denervation and cocaine not shown).
cocaine treatment derived from Guimaraes et al.\textsuperscript{2} Treatment with 5-OHDA, however, did not prolong the T_{1/2}, suggesting that neuronal uptake was not altered by this agent.

In time control strips, no change in the response to tyramine was observed. In contrast, treatment of strips with either 5- or 6-OHDA markedly reduced responses to tyramine (Fig. 4). 6-OHDA more completely abolished responses to tyramine than did 5-OHDA (Fig. 4).

Responses to acetylcholine, a nonadrenergic agonist, were highly variable (Fig. 5, control panel). These responses did not appear to be significantly altered by treatment with 6- and 5-OHDA (Fig. 5).

**Influence of 6-OHDA on Contractile Responses to 5-OHDA**

5-OHDA elicited a large, rapidly developing contraction (Fig. 2). In an attempt to suggest a mechanism for this apparent sympathomimetic response (i.e., direct or indirect) and to validate partially 6-OHDA treatment as a useful in vitro method, the influence of 6-OHDA treatment on partial CRC for 5-OHDA (10^{-6}, 10^{-5}, 10^{-4} M) was determined. CRCs for 5-OHDA were determined before and after a treatment period in strips treated as time control or with 6-OHDA. As shown in Figure 6, responses of the time control group of strips to 5-OHDA were similar, or slightly enhanced, after the treatment period. Responses to 5-OHDA in strips treated with 6-OHDA were significantly reduced. However, these responses were not reduced to the same extent as were responses to tyramine (Fig. 4).

**Discussion**

These experiments demonstrate that 5- and 6-OHDA have several effects on isolated canine saphenous veins. Each agent produces an initial contraction and subsequent inhibition of contractile responses to transmural nerve stimulation and tyramine. The effects of 6-OHDA on adrenergic function have been studied in experiments in which animals have received the drug and when isolated tissues have been incubated with 6-OHDA.\textsuperscript{4} Studies in tissues from animals treated with 6-OHDA have shown that responses to transmural nerve stimulation were inhibited whereas responses to norepinephrine were enhanced.\textsuperscript{10, 11, 13, 20-23} However, in vitro application of 6-OHDA produced only transient effects on responses to transmural stimulation in rat mesenteric artery, cat heart, and nictitating membrane.\textsuperscript{10} Spontaneous oxidation of 6-OHDA was observed in these experiments.\textsuperscript{10} In a more recent in vitro study, the effects of 6-OHDA were investigated in rat portal vein and caudal artery.\textsuperscript{13} In these experiments, spontaneous oxidation of 6-OHDA was prevented by lowering pH and adding glutathione to the vehicle.\textsuperscript{13} When oxidation was prevented, the effects of 6-OHDA were not transient but were consistent with results of earlier studies.\textsuperscript{10, 11, 13, 20-23} It was suggested therefore that 6-OHDA could be useful for in vitro production of a functional adrenergic denervation.\textsuperscript{13}

Results of our study show that in vitro application of 6-OHDA will functionally denervate the canine saphenous vein. Auto-oxidation of 6-OHDA was not prevented, and the nature of the active form of the drug in vivo and in vitro is unknown.\textsuperscript{1} The effects of 6-OHDA were reproducible, blocked by DMI, and not transient, suggesting that it may not be necessary to prevent visible auto-oxidation.
of 6-OHDA in order to produce functional denervation in all adrenergically innervated tissues.

Earlier studies showed that 6-OHDA was an indirectly acting sympathomimetic agent. In the present study, 6-OHDA elicited a small transient contraction which was followed by a slowly developing sustained contraction. The small initial transient contraction was only partially inhibited by DMI, whereas the slowly developing sustained contractile response was blocked by DMI. These findings suggest that the transient response may be due to a direct effect of 6-OHDA or a breakdown product on venous smooth muscle. In the present study, application of 6-OHDA abolished contractile responses to transmural stimulation and tyramine, and these effects were associated with a marked reduction in norepinephrine levels in the saphenous vein. These data suggest that 6-OHDA, or a breakdown product, is actively taken up by adrenergic terminals and interferes with nerve function by depleting nerve terminal stores of norepinephrine.

Our data suggest that the functional correlate of the depletion process is the sustained contraction of the vein which is easily monitored in the smooth muscle bath. In addition to abolishing responses to nerve stimulation and tyramine, 6-OHDA prolonged the T1/2 of the response to norepinephrine. The increased duration of the response to norepinephrine suggests that 6-OHDA may interfere with uptake of norepinephrine by nerve terminals in the saphenous vein. This agent has been shown to block uptake of norepinephrine in rat portal vein and caudal artery.

Early during treatment periods, 6-OHDA reduced response to transmural nerve stimulation, and this action was not blocked by DMI. Moreover, this initial inhibition of neurogenic responses may be due to an early partial alpha-blocking effect. It is also possible, but doubtful, that prejunctional inhibitory alpha receptors may be stimulated by 6-OHDA.

In the anesthetized dog, 5- and 6-OHDA have similar effects on nerve terminal function in the pulmonary vascular bed. However, the effects of 5-OHDA on nerve terminal function have not been studied in isolated vascular smooth muscle preparations. Our experiments show that the effects of 5- and 6-OHDA differ in some respects in the saphenous vein. Exposure to 5-OHDA produced a large increase in contractile tension which spontaneously declines to a steady level above initial baseline value. Repeated additions of 5-OHDA to the bath gave progressively smaller peak contractions suggestive of tachyphylaxis. Following treatment with 5-OHDA, responses to transmural nerve stimulation were completely inhibited, whereas responses to tyramine were markedly attenuated. These findings suggest that contractions elicited by 5-OHDA correlate with release of norepinephrine from adrenergic terminals caused by 5-OHDA or its breakdown products. Although both 5- and 6-OHDA completely abolished responses to transmural nerve stimulation, the effects of these agents on responses to tyramine and norepinephrine were different. Responses to tyramine were inhibited to a lesser extent by 5-OHDA, and this agent did not influence the T1/2 of responses to norepinephrine.

These data suggest that, in the saphenous vein, 5-OHDA has a lesser effect than 6-OHDA upon uptake and/or on the tyramine-releasable pool of transmitter. In addition, pretreatment of strips with 6-OHDA only partially inhibited subsequent responses to 5-OHDA; this suggests that 5-OHDA may have more direct action on venous smooth muscle than 6-OHDA.

The results of our experiments suggest that both 5- and 6-OHDA are useful pharmacological interventions for studying adrenergic mechanisms in vascular smooth muscle preparations in vitro. The experiments suggest that, after treatment with 5-OHDA, responses may be studied in vessels with adrenergic nerves that no longer respond to transmural stimulation but which still may have other neuronal activity such as amine uptake. Treatment with 6-OHDA should provide a more complete loss of nerve terminal function in isolated vessels.

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Diet and Sire Effects on Serum Cholesterol and Cholesterol Absorption in Infant Baboons (Papio cynocephalus)

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SUMMARY One hundred three baboon infants, the progeny of an equal number of dams and seven sires, were breast fed or were fed prepared formulas containing 1.2, 29, or 61 mg/dl cholesterol for 14 weeks. We measured serum cholesterol and triglyceride concentrations at birth and at 3-week intervals, and cholesterol absorption at 12 weeks. Dietary cholesterol had a significant effect on serum cholesterol concentration at 12 weeks and on cholesterol absorption, but did not affect weight or serum triglyceride concentration. Sire had a significant effect on serum cholesterol concentration at birth and at 12 weeks, but the effect at birth did not predict the effect at 12 weeks. Sire did not affect cholesterol absorption, serum triglyceride concentration, or weight at 12 weeks. The sire effect on serum cholesterol concentration in infancy is not mediated by control of cholesterol absorption. Males weighed more than females at 12 weeks, but sex did not affect serum cholesterol concentration, triglyceride concentration, or cholesterol absorption.

The serum cholesterol concentration of children in the United States increases from an average of 75 mg/dl at birth to about 180 mg/dl at 18 years, and most of the increase occurs in the first year of life. Since atherosclerosis begins in childhood and progresses rapidly in the second and third decades of life, and since control of hypercholesterolemia is widely regarded as essential to long range prevention of atherosclerotic disease, it is important to determine the factors controlling serum cholesterol concentration in infancy and childhood. Therefore, we have undertaken a long-term study of the influence of infant, juvenile, and adult diet and heredity on cholesterol metabolism and atherosclerosis in the baboon (Papio cynocephalus). The baboon is a large nonhuman primate with many physiological characteristics similar to those of man, including particularly its cholesterol metabolism and its serum cholesterol response to an atherogenic diet. We report here the results of the first phase of the experiment: the effects of diet, sire, and sex on serum lipid concentrations, cholesterol absorption, and growth in 103 baboon infants from birth to 12 weeks of age.

Methods

Breeding Colony and Infant Accession

One hundred-twenty female baboons were randomly assigned to six outdoor gang-caged groups with one male in each group. We determined the...
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