Up-regulation of endothelial stretch-activated cation channels by fluid shear stress

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Abstract

Objective: Stretch-activated cation channels (SAC) have been suggested to act as endothelial mechanosensors for hemodynamic forces. Ca²⁺ influx through SAC could induce an intracellular Ca²⁺ signal stimulating Ca⁴⁺-dependent synthesis of vasodilators like NO, prostacyclin, or EDHF. In the present study we tested whether laminar shear stress (LSS) regulates SAC function. Methods: Electrophysiological properties of SAC were investigated in human umbilical vein endothelial cells (HUVEC) subjected to defined levels of LSS in a flow-cone apparatus. Results: In HUVEC, we identified a Ca²⁺ permeable SAC that was activated by membrane stretch. Single-channel current densities of SAC in cell-attached patches were significantly increased in HUVEC exposed to an LSS of 5 dyn/cm² for 4 h (1.15 ± 0.17 SAC/patch) compared to HUVEC kept in stationary culture (0.46 ± 0.07 SAC/patch). Exposure of HUVEC to a higher LSS of 15 dyn/cm² for 4 h induced similar up-regulation of SAC (1.27 ± 0.21 SAC/patch). After 24 h exposure to LSS of 15 dyn/cm², single-channel current densities of SAC remained up-regulated (1.07 ± 0.18 SAC/patch) compared to controls. In addition, stretch-sensitivity of SAC (channel activity NP at –30 mmHg) significantly increased after 2 h of exposure to LSS of 5 and 15 dyn/cm² and remained up-regulated after 24 h. Inhibition of protein kinases and tyrosine kinases by H7 and genistein, respectively, prevented LSS-induced alteration of SAC function. Conclusion: Single-channel current density and mechanosensitivity of SAC in HUVEC is up-regulated by LSS. Up-regulation of SAC function leads to enhanced mechanosensitive Ca²⁺ influx, and represents a novel adaptive mechanism of the endothelium in the presence of altered hemodynamic forces. © 2002 Elsevier Science B.V. All rights reserved.

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1. Introduction

Shear stress plays a crucial role in the regulation of vascular tone [1]. In the mechanism of mechanotransduction, the endothelium acts as the signal transduction interface, converting physical forces into intracellular biochemical signals and subsequent release of vasoactive substances [2]. Exposure of endothelial cells to shear stress leads to release of nitric oxide [3,4], increased expression of endothelial nitric oxide synthase (NOSIII) [5,6], and rearrangement of the actin cytoskeleton [7] within hours. In the very early cellular responses of mechanotransduction, increases of the intracellular Ca²⁺ concentration [8–10] and activation of ion fluxes across the cell membrane are involved [9,11,12]. Especially increases of the intracellular Ca²⁺ concentration ([Ca²⁺]) has been thought to play a key role in signal transduction events elicited by acute elevation of fluid shear stress [13,14] since an increase in [Ca²⁺] stimulates the Ca²⁺-dependent synthesis of vasodilators such as nitric oxide and prostacyclin [4,15,16]. This increase in [Ca²⁺] is thought to be due to the release of Ca²⁺ from internal stores [9,12,14] and the...
influx of extracellular Ca$^{2+}$ across the cell membrane [13]. Presumably the mechanosensitive Ca$^{2+}$ influx is mediated by the activation of stretch-activated cation channels (SAC). Such SAC have been identified in vascular endothelial cells and therefore might act as microsensors for changes in hemodynamic forces [17,19,20].

In experimental and human hypertension, the endothelium is exposed to increased hemodynamic forces. In previous studies, we showed that alterations of SAC function occurred in genetically hypertensive rats as well as in human hypertension [17,21]. However, the mechanisms leading to increased SAC function have not been defined so far. We hypothesized that increased levels of fluid shear stress leads to these alterations in SAC function. To test this hypothesis, we performed an electrophysiological study to determine SAC function in human umbilical vein endothelial cells (HUVEC) exposed to defined laminar shear stress (LSS) of different magnitude and duration.

2. Materials and methods

2.1. Cell culture and shear stress experiments

HUVEC were isolated and cultured as described previously. Briefly, umbilical cord veins were rinsed with PBS without Ca$^{2+}$ and Mg$^{2+}$, filled with 2.5% trypsin and incubated for 1 h. Endothelial cells were then harvested and transferred to cell culture flasks. Cells were cultivated in endothelial cell growth medium (Promocell, Heidelberg, Germany) containing 2% FCS, 0.4% ECGS/H, 0.1 ng/ml EGF, 1 ng/ml bFGF, and 1 µg/ml hydrocortisone.

For shear stress experiments, HUVEC of second passage were grown to confluence in petri dishes. One day after reaching confluence, HUVEC were subjected to LSS in a cone-and-plate viscometer [22].

The viscosimeter consists of a cone with an angle of 0.5° rotating on top of a 94×16 mm cell culture dish. LSS of 5 dyn cm$^{-2}$ and 15 dyn cm$^{-2}$ was applied for 2, 4, and 24 h by a constant angular velocity in a humidified environment with 5% CO$_2$ at 37°C. Then, 5% dextran (M$_w$ 71,400) was added to the cell culture medium to increase the viscosity of the medium 2.95-fold to 0.02065 dyn s cm$^{-2}$. The angular velocity of the cone was 6.34 s$^{-1}$ for 15 dyn/cm$^2$ and 2.11 s$^{-1}$ for 5 dyn/cm$^2$. Each cell culture dish exposed to LSS was accompanied by a control sample from the same HUVEC preparation incubated with cell culture medium supplemented with dextran 5% for the same period of time (2, 4, and 24 h) but in the absence of LSS.

2.2. Patch-clamp experiments

Patch-clamp experiments were carried out as described before [17]. Single channel membrane currents were recorded with an EPC-9 (HEKA, Lambrecht, Germany) patch-clamp amplifier, low-pass filtered (−3 dB, 1000 Hz) at a sampling time of 0.5 ms. Patch pipettes were pulled from borosilicate glass capillaries with 0.3 mm wall thickness and had a tip resistance of 4 MΩ in symmetric KCl solution. All experiments were performed at room temperature. In the displayed current traces, single channel currents carried by cations moving from the extracellular to the intracellular side are depicted as downward (negative) currents.

If not stated otherwise, in single-channel recordings the patch pipette solution contained (in mmol/l): 140 KCl, 1 CaCl$_2$, 1 MgCl$_2$, and 10 HEPES (pH 7.4). BaCl$_2$ pipette solution contained (in mmol/l) 90 BaCl$_2$, and 10 HEPES (pH 7.4) and CaCl$_2$ pipette solution (in mmol/l) 90 CaCl$_2$, and 10 HEPES (pH 7.4). NaCl pipette solution contained (in mmol/l) 140 NaCl, 1 CaCl$_2$, 1 MgCl$_2$, and 10 HEPES (pH 7.4). The bath solution contained normal saline solution (in mmol/l): 140 NaCl, 4.3 KCl, 1.3 CaCl$_2$, 1 MgCl$_2$ and 10 HEPES at pH 7.4. In patch-clamp experiments, mechanical stimulation of the cell membrane to induce SAC activation was performed by applying negative hydrostatic pressures to the rear of the patch pipette. The hydrostatic pressure was adjusted and controlled with a water manometer and monitored with a differential pressure transducer.

Channel conductance values were calculated by linear regression of current to voltage data.

As a quantitative measure of SAC function in the cell membrane of HUVEC subjected to LSS or kept in stationary culture, we determined the number of single SACs (single-channel current density) in cell-attached patches at −90 mV by counting the number of current amplitudes: in multi-channel patches, we thus assessed the maximum number of superimposed openings of SACs during mechanical stimulation (−30 mmHg pipette pressure). We performed a total of 199 cell-attached patch-clamp experiments in HUVEC subjected to LSS and 247 experiments in controls, respectively. Additional series of experiments were conducted in the presence of 50 µM H7, an inhibitor of protein kinases PKA, PKC and PKG and 50 µM genistein, an inhibitor of tyrosine kinases.

For comparison of stretch-sensitivity of SAC in cells subjected to shear stress and in controls, single channel activity induced by first mechanical stimulation with −30 mmHg pipette pressure were analyzed and we calculated NP$_2$ values, mean open times and mean closed times as described previously [18].

SAC function was determined immediately after shear stress exposure and only tight-seal patch-clamp experiments with a seal resistance of more than 4 GΩ were included in the statistical analysis.

2.3. Inhibition of tyrosine kinases and protein kinases

H7 was dissolved in ethanol/water (1/1) and genistein in 99% DMSO, respectively, to make a 100 mM stock solution. Both inhibitors were added to cell culture
medium resulting in a final concentration of 50 μM immediately before onset of LSS.

For controls, 50 μM H7 or genistein were added to the cell culture medium. SAC function was measured after 4 h and after washout of inhibitors.

In an additional set of experiments, SAC densities were determined directly in the presence of genistein or H7 without LSS exposure.

2.4. Reagents

All chemicals were purchased from Sigma (Deisenhofen, Germany). Cell culture reagents were obtained from Biochrom (Berlin, Germany) and cell culture medium was purchased from Promocell (Heidelberg, Germany).

2.5. Statistics

Unless otherwise indicated, data are given as mean±S.E. Statistical evaluation was performed using Student’s t-test for unpaired data. Values of P<0.05 were considered statistically significant.

3. Results

3.1. SAC in HUVEC

Cell-attached patch clamp recordings from HUVEC usually were without spontaneous channel activity. Stretching the patch-clamped cell membrane by applying negative pressure to the rear of the patch pipette evoked activation of SAC. Channel activity measured as the probability of a channel being open (NPo) depended on the degree of membrane stretch: SAC activity in HUVEC gradually increased when negative pipette pressure was increased in a range from -10 to -50 mmHg (Fig. 1A) with a mean NPo of 0.41±0.08 at -30 mmHg (n=18) and an NPo of 1.1±0.09 at -50 mmHg (n=35).

Increases in channel activity (NPo) after exposure to LSS were due to a significant decrease in mean closed time (34.5 ms±8.2, n=6 for controls vs. 10.4 ms±5.1, n=8 after exposure to LSS, P<0.05), with no significant changes in mean open time (7 ms±1.2, n=6 for controls vs. 17.2 ms±7.4, n=8 after exposure to LSS, P=0.22).

Channel activity immediately ceased when membrane stretch was relieved and could be stimulated repeatedly, although SAC activity showed a rapid rundown after repetitive mechanical stimulation (Fig. 1B).

Mean channel conductance of SAC in cell-attached patches in HUVEC was 33±2 pS (n=13) for K⁺ and 29±3 pS (n=3) for Na⁺. The channel was also permeable for divalent cations. At negative clamping potentials and with a pipette solution containing 90 mM Ba²⁺ or Ca²⁺ as charge carrier, the channel had a mean conductance for Ba²⁺ of 14±2 pS (n=3) and 11±3 pS (n=4) for Ca²⁺ (Fig. 1C–E). A considerable current rectification of single channel currents through SAC was not detected in a voltage range from −100 to +100 mV. Moreover, SAC lacked apparent voltage dependence.

3.2. SAC function after shear stress exposure

To investigate regulation of SAC function by LSS, HUVEC were exposed to 5 and 15 dyn/cm² of LSS for 2, 4, and 24 h or kept in stationary culture as control. Exposure to LSS led to morphological changes in HUVEC. Elongation of cells could first be observed after 4 h of LSS and was pronounced after 24 h of LSS (Fig. 2).

Single channel-current densities of SAC in the patch-clamped membranes were significantly increased in HUVEC exposed to shear stress compared to control HUVEC kept in stationary culture: after 2 h of LSS, SAC-current density at −90 mV was increased to 0.92±0.17 SAC/patch at 5 dyn/cm² (P<0.01; n=36) and to 0.96±0.25 SAC/patch at 15 dyn/cm² (P<0.01; n=24) compared to controls (0.46±0.07 SAC/patch; n=93).

SAC density further increased after 4 h of LSS to 1.15±0.16 SAC/patch at 5 dyn/cm² (P<0.01; n=34) and to 1.27±0.21 SAC/patch at 15 dyn/cm² (P<0.01, n=33) compared to controls (0.39±0.07 SAC/patch; n=83).

After 24 h exposure to high LSS of 15 dyn/cm², SAC density remained up-regulated (1.07±0.18 SAC/patch; P<0.01; n=42) compared to controls (0.51±0.11 SAC/patch; n=71). However, after 24 h exposure to low LSS of 5 dyn/cm², SAC density tended to reverse to control levels (0.77±0.19 SAC/patch, n=30; n.s.) (Fig. 3A).

Stretch-sensitivity of SAC was also altered by LSS. In controls, probability of a channel being open (NPo) was 0.41±0.08 at −30 mmHg (n=16). After 2 h exposure to LSS of 5 dyn/cm², stretch-sensitivity was elevated (NPo=0.95±0.15, P<0.01, n=7) and was further increased after 4 h (NPo=0.91±0.24, P<0.01, n=9). After 24 h LSS of 5 dyn/cm², stretch-sensitivity remained up-regulated (NPo=0.83±0.11, P<0.01, n=6). Similarly, after exposure to LSS of 15 dyn/cm², probability of a channel being open was higher after 2 h (NPo=0.96±0.3, P<0.05, n=4), after 4 h (NPo=1.2±0.3, P<0.01, n=8), and after 24 h (NPo=1.1±0.21, P<0.01, n=7), when compared to controls (Fig. 4A and B). Single channel conductance of SAC was not different between HUVEC exposed to LSS (35.4±4 pS, n=10) and HUVEC kept in stationary culture (33.3±2 pS, n=13).

3.3. Effect of kinase inhibition on LSS-induced SAC regulation

In an additional set of experiments we tested the effect of protein kinase and tyrosine kinase inhibition on SAC regulation by LSS.

In the presence of genistein SAC densities showed only a slight tendency to be elevated after exposure to LSS of 15 dyn/cm² for 4 h (0.68±0.12 SAC/patch, n=47).
Fig. 1. (A) Gradual increase of channel activity of stretch-activated cation channel (SAC) in HUVEC in response to negative pipette pressure. A total of three SAC was simultaneously activated in this cell-attached patch. Channel openings in the downward direction indicate K currents flowing from the pipette into the cell. Activation was immediately reversed after cessation of negative pipette pressure. Pipette solution contained (in mmol/l): 140 KCl, 1 CaCl₂, 1 MgCl₂, and 10 HEPES (pH 7.4). (B) Adaptation of SAC mechanosensitivity after repetitive mechanical stimulation. Representative current-recordings of SAC stimulated repetitively by 30 mmHg pipette pressure in intervals of 2 s (upper trace) and after 1 min without stimulation (lower trace) at a holding potential of -90 mV in cell-attached patches. Pipette solution contained (in mmol/l): 140 KCl, 1 CaCl₂, 1 MgCl₂, and 10 HEPES (pH 7.4). (C) Ba²⁺ influx through SAC in HUVEC. Channel openings in the downward direction indicate Ba²⁺ currents flowing from the pipette into the cell at a holding potential of -90 mV. Pipette solution contained (in mmol/l): 90 BaCl₂, and 10 HEPES (pH 7.4). (D) Ca²⁺ influx through SAC in HUVEC. Channel openings in the downward direction indicate Ca²⁺ currents flowing from the pipette into the cell at a holding potential of -90 mV. Pipette solution contained (in mmol/l): 90 CaCl₂, and 10 HEPES (pH 7.4). (E) Current–voltage (I–V) relationship of SAC in cell-attached patches was determined in the presence of the following pipette solutions: open squares, K⁺; filled squares, K⁺ after exposure to LSS; filled circles, Na⁺; filled triangles, Ba²⁺; open triangles, Ca²⁺.

Although, when compared to controls incubated with genistein for 4 h without exposure to LSS (0.47±0.17 SAC/patch, n=23) there was no statistically significant difference (P=0.36). These SAC densities are significantly lower compared to SAC densities after LSS of 15 dyn/cm² for 4 h without inhibition of protein phosphorylation (1.27±0.21 SAC/patch, n=33, P<0.01).

When cells were incubated with H7 we observed a lower SAC density compared to controls, which however was not statistically significant (0.82±0.14 SAC/patch, n=35 after exposure to LSS of 15 dyn/cm² vs. 0.41±0.13 SAC/patch in controls, n=24, P=0.051) (Fig. 3B).

To test whether there are direct inhibitory effects of both substances on SAC function we performed experiments measuring SAC densities and function in the presence of H7 or genistein. Here, neither H7 nor genistein had a detectable effect on SAC density (H7: 0.4±0.22 SAC/patch, n=10, P=0.77; genistein: 0.44±0.14 SAC/patch, n=18, P=0.51). Stretch-sensitivity of SAC after exposure to LSS was not altered by genistein treatment (NPo 0.60±0.08, n=12) when compared to controls (NPo 0.40±0.08, n=7, P=0.13).

After inhibition of protein kinases by H7, stretch-sensitivity of SAC was still enhanced after LSS of 15 dyn/cm² for 4 h (NPo 0.67±0.04, n=14) compared to controls incubated with H7 without LSS exposure (NPo 0.28±0.04, n=7, P<0.01) (Fig. 4C). However, stretch-sensitivity of SAC after exposure to LSS is significantly lower after
Fig. 1. (continued)
Fig. 2. Morphology of HUVEC in stationary culture and after 4 and 24 h of laminar shear stress (LSS) of 15 dyn/cm². Significant cell elongation occurred after 4 h of LSS in the direction of flow as indicated by arrow. HUVEC were markedly elongated after 24 h of LSS.

Fig. 3. (A) Single-channel current densities of SAC (SAC/patch at −30 mmHg pipette pressure) in HUVEC after exposure to laminar shear stress (LSS) and in stationary culture. (B) Single-channel current densities of SAC (SAC/patch at −30 mmHg pipette pressure) in HUVEC after exposure to laminar shear stress (LSS) of 15 dyn/cm² and in stationary culture with inhibition of tyrosine kinases and protein kinases. Channel activity was measured at a holding potential −90 mV in cell-attached patches. Data are given as mean±S.E., * P<0.01, Student’s t-test.
Fig. 4. Up-regulation of mechanosensitivity of SAC after exposure to laminar shear stress (LSS). (A) Representative current-recordings of SAC at −30 mmHg pipette pressure in HUVEC exposed to LSS of 15 dyn/cm² for 24 h and in stationary culture. c→, closed state of channels. Channel activity was measured at a holding potential −90 mV in cell-attached patches. Pipette solution contained (in mmol/l): 140 KCl, 1 CaCl₂, 1 MgCl₂, and 10 HEPES (pH 7.4). (B) Open probabilities (NP₀) of SAC after exposure to LSS and in stationary culture. Data are given as mean±S.E., *P<0.05, **P<0.01, Student’s t-test. (C) Open probabilities (NP₀) of SAC after exposure to LSS of 15 dyn/cm² for 4 h with inhibition of tyrosine kinases or protein kinases. Data are given as mean±S.E., *P<0.05, Student’s t-test.
incubation with H7 or genistein when compared to results after 15 dyn/cm² for 4 h without H7 (NP, 1.2±0.31, P<0.01, n=12).

4. Discussion

In our study we characterized a SAC in HUVEC and tested whether SAC function is altered by LSS. With respect to single channel conductance, cation selectivity, Ca²⁺-permeability, and mechanosensitivity, SAC in HUVEC resembles the characteristics of a SAC previously identified in endothelium of tissue slices from human umbilical veins and in the endothelial cell line EA.hy 926 [21]. SAC with similar properties have also been identified in cultured endothelial cells from neonatal pig aorta [19], intact porcine endothelium from atrial endocardium [23] and brain capillaries [24], as well as in intact endothelium preparations of rat aorta [17].

The major finding of this study is that LSS is an important regulator of SAC function in endothelial cells. We could show that mechanosensitivity as well as density of SAC in HUVEC is enhanced after exposure to LSS: after 2 and 4 h exposure to LSS, SAC density was two- to threefold increased when compared to controls kept in stationary culture. Moreover, after 24 h of LSS SAC density remained elevated. In addition to alterations in SAC density, mechanosensitivity of SAC was almost doubled after exposure to LSS for 2, 4, and 24 h. With respect to alteration of mechanosensitivity of SAC, previous studies have shown that rearrangement of the actin-cytoskeleton or phosphorylation of the channel protein possibly mediate changes in stretch-sensitivity of SAC [25–27] similar to epithelial sodium channels [28,29]. Therefore, LSS-induced alterations of endothelial SAC function could be explained by early cytoskeletal rearrangement.

It has been shown in previous studies that disruption of cytoskeletal structures leads to an inactivation of SAC function [25,30] indicating that an intact cytoskeleton is crucial for SAC function as well as endothelial mechanosensing of shear stress [31]. However, cytoskeletal disruption completely abolishes SAC function in endothelial cells, unfortunately preventing a further investigation of whether alterations of SAC function are caused by an altered coupling of the channel to cytoskeletal elements.

In the underlying mechanisms of shear stress-mediated alterations in ECs, protein phosphorylation has been shown to play a role. For instance, protein kinase C inhibition significantly attenuated the induction of c-fos as well as shear stress-induced PDF gene induction. Inhibition of tyrosine kinases has been shown to suppress NF-κappaB-induced promoter activity in response to shear stress [32–35]. In contrast, shear stress-induced eNOS up-regulation was found to be independent of protein phosphorylation [36]. With respect to alterations of SAC densities and function, phosphorylation seems to be involved as inhibition of tyrosine kinases and protein kinases prevented upregulation of SAC density and attenuated increase of SAC function after exposure to LSS. Therefore, protein phosphorylation might be an important signal transduction step in regulating SAC expression or integration of the channel into the cell membrane.

Alterations in SAC function in HUVEC were observed before first macroscopic signs of cell elongation occurred. Thus, SAC up-regulation and increase in stretch-sensitivity did not seem to be a direct consequence of shear stress-induced cell elongation. Generally, this is the first study which shows alteration of ion channel regulation as a consequence of exposure to LSS.

In previous studies, SAC function has been shown to be altered in hypertension and preeclampsia associated with increased hemodynamic forces [37]. In vessel preparation from human umbilical veins of pregnancies complicated by preeclampsia, apparent endothelial SAC density was almost doubled compared to SAC density in normal pregnancies [21]. Furthermore, an increased SAC function was observed in adult spontaneously hypertensive rats (SHR) compared to Wistar-Kyoto (WKY) rats [17]. Later changes in ion channel properties were interpreted as a consequence rather than a cause of hypertension as they could exclusively be found in rats with established hypertension [17]. However, the mechanism leading to such alterations in SAC function in endothelial cells have not been defined so far. In the present in vitro study, SAC density showed a two- to threefold increase depending on the magnitude of LSS. This increase of SAC density was similar to increases of SAC densities found in experimental hypertension. This might indicate that LSS is involved in up-regulation of SAC in hypertension. In addition, we could show that up-regulation of SAC after exposure to LSS was paralleled by a twofold increase in stretch-sensitivity. With respect to alterations in mechanosensitivity of SAC in experimental hypertension, a similar increase of stretch-sensitivity was observed in SHR [17].

In hypertension, up-regulation of Ca²⁺-permeable SAC was interpreted as a compensatory mechanism of the endothelium to enhance Ca²⁺-influx and thereby formation of vasodilating factors in the presence of increased hemodynamic forces. Such alterations in endothelial calcium signaling in hypertension have also been reported by others. For instance, in endothelial cells of hypertensive rats, basal [Ca²⁺], is significantly higher compared to normotensive rats [38,39]. Moreover, flow-pretreatment enhanced endothelial [Ca²⁺], response in aortas from normotensive rats by increasing calcium influx [13]. It is tempting to speculate that these alterations in endothelial Ca²⁺ homeostasis is mediated by increased SAC function.

In the present study, SAC density remained up-regulated after 24 h exposure to high LSS (15 dyn/cm²). However, at lower LSS (5 dyn/cm²) a tendency towards reversal of SAC up-regulation was observed. This might indicate that
lower rates of prolonged LSS transiently increase SAC function whereas higher rates of prolonged LSS apparently leads to persisting alterations in SAC function. Such persisting high levels of LSS are present in hypertension. Therefore, up-regulation of SAC as previously observed in experimental and human hypertension could be due to constantly elevated levels of LSS.

5. Conclusion

In HUVEC, exposure to LSS leads to an elevated SAC-function which could increase mechanosensitive Ca\(^{2+}\) entry. This increase in SAC function may represent a novel adaptive mechanism of the endothelium in the presence of increased LSS as elevated Ca\(^{2+}\)-influx could stimulate synthesis of vasoactive factors to induce vasodilation and thereby to reduce shear stress. The persistent up-regulation of SAC at high LSS might be an important counterregulatory mechanism at increased hemodynamic forces.

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References


