Advanced glycation end products delay corneal epithelial wound healing through reactive oxygen species generation

Long Shi · Hongmei Chen · Xiaoming Yu · Xinyi Wu

Abstract Delayed healing of corneal epithelial wounds is a serious complication in diabetes. Advanced glycation end products (AGEs) are intimately associated with the diabetic complications and are deleterious to the wound healing process. However, the effect of AGEs on corneal epithelial wound healing has not yet been evaluated. In the present study, we investigated the effect of AGE-modified bovine serum albumin (BSA) on corneal epithelial wound healing and its underlying mechanisms. Our data showed that AGE-BSA significantly increased the generation of intracellular ROS in telomerase-immortalized human corneal epithelial cells. However, the generation of intracellular ROS was completely inhibited by antioxidant N-acetyl-cysteine (NAC), anti-receptor of AGEs (RAGE) antibodies, or the inhibitor of NADPH oxidase. Moreover, AGE-BSA increased NADPH oxidase activity and protein expression of NADPH oxidase subunits, p22phox and Nox4, but anti-RAGE antibodies eliminated these effects. Furthermore, prevention of intracellular ROS generation using NAC or anti-RAGE antibodies rescued AGE-BSA-delayed epithelial wound healing in porcine corneal organ culture. In conclusion, our results demonstrated that AGE-BSA impaired corneal epithelial wound healing ex vivo. AGE-BSA increased intracellular ROS generation through NADPH oxidase activation, which accounted for the delayed corneal epithelial wound healing. These results may provide better insights for understanding the mechanism of delayed healing of corneal epithelial wounds in diabetes.

Keywords AGEs · ROS · NADPH oxidase · Cornea · Wound healing

Introduction Diabetes is a public health problem of considerable magnitude [1]. Delayed healing of corneal epithelial wounds is regarded as a serious complication of diabetes [2]. Proper healing of corneal epithelial wounds is vital for maintaining a clear, healthy cornea and preserving vision. Delayed healing of corneal epithelial wounds might cause sight-threatening complications, such as ocular surface irregularity, microbial keratitis, or even blindness. Delayed healing of corneal epithelial wounds in diabetes is still a challenging disease to treat because the mechanism of the disease is not yet fully understood [3]. Therefore, delineating the underlying mechanisms of delayed corneal epithelial wound healing in diabetes is urgently required to identify potential preventative and therapeutic strategies.

Advanced glycation end products (AGEs) play a crucial role in the development of diabetic complications [4]. AGEs are a heterogeneous group of irreversible adducts from glucose–protein condensation reactions, as well as lipids and nucleic acids exposed to reducing sugars [5]. The formation and the accumulation of AGEs have been demonstrated to progress at an accelerated rate under diabetic conditions [6].