Special Issue

Approach to Dry Eye in Video Display Terminal Workers (Basic Science)

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The use of video display terminals (VDT) and staring at screens of technologic devices, including desktops, laptops, tablets, and smartphones have become ubiquitous in a wide range of age groups because of the rapid advance of network culture-mediated communications. The incidence of dry eye is particularly high in workers that work with VDT. To facilitate an understanding of the mechanisms of VDT-associated dry eye, as well as to develop novel treatment approaches, a VDT worker dry eye model was created. The procedure involved placing rats on a swing in combination with exposure to an evaporative environment. This animal model reveals that the blink frequency was reduced to one-third of the nonswing riding levels, which is similar to the results that have been reported by VDT users. Pathologic analysis of the lacrimal gland in this dry eye model showed that the decrease in tear secretion was accompanied by a decrease in the acinar cell number, and an enlargement of acinar cells was accompanied by filling with an increased volume of secretory vesicles and a loss of intracellular cell structure, suggesting the involvement of lacrimal hypofunction. An interventional study using this dry eye model showed that oral supplementation of some natural ingredients is a possible therapy for relieving symptoms of VDT-associated dry eye. Further investigations for the establishment of VDT use–associated dry eye models that may be used to evaluate ocular discomfort that mimic the condition in humans are needed to understand and modify this type of dry eye.

Keywords: dry eye, lacrimal gland, oxidative damage

The incidence of dry eye is markedly increasing in relation to the radical expansion in global internet networks and network culture-mediated communications.[1] People routinely using video display terminals (VDT) have demonstrated a higher incidence of musculoskeletal disorders and eyestrain; the daily, habitual use of electronic communication devices, such as desktop and laptop computers, tablets, and smartphones, are accepted as the possible causes of the symptoms.[2,3] The results of a web-based self-screening questionnaire of dry eye in general internet users showed that 36% of respondents reported dry eye symptoms.[4] A cross-sectional study in Japanese young and middle-aged office workers using VDT revealed that dry eye status is associated with lower work productivity and impaired work performance.[5]

Animal models are essential tools to facilitate our understanding of the mechanisms of disease, as well as to develop novel treatment approaches. An extensive effort has been made to develop suitable experimental procedures that mirror the pathophysiologic alterations in the ocular surface and/or lacrimal function in dry eye. Experimental models include animals that undergo botulinum toxin B injections to the lacrimal gland (LG) to inhibit secretory function,[6,7] trigeminal or parasympathetic nerve ablation that interrupts neural stimulation to the LG,[8] and vitamin deficiency[9] that induced corneal epitheliopathy, among others.

Well-established popular animal models are those that undergo extraorbital LG excision[10] and combined systemic anticholinergic drug scopolamine administration with desiccating controlled environmental stress.[11] These models not only induce chronic tear deficiency with epitheliopathy but also increase tear proinflammatory cytokines and activate mucosal immune responses that are characteristic of human dry eye symptoms.

Animal Model of VDT Worker Dry Eye Model

VDT work, any of various tasks that involve gazing at a liquid crystal or cathode ray tube display, is characterized by a lack of blinking, low-humidity occupational environment, and sustained static postures during repetitive tasks.[12] Based on the concept that gazing is necessary in the spatial orientation that is required for the maintenance of posture, we developed a novel procedure involved placing rats on a swing (Fig. 1A), similar to that observed in tightrope walkers, in combination with exposure to an evaporative environment to simulate humans in VDT work.[13] In this dry eye model, to simulate the work-rest-sleep cycle of office workers on a daily basis, each rat remained in place on the swing made of plastic piping for 8 h/d between 9 AM and 5 PM with 30 minutes of resting for access food and water. For the remaining 16 hours, they were individually placed in cages with water and food ad libitum (Fig. 1B) To prevent the rat from slipping off the swing, the swing was suspended 60 cm above the bottom and 30 cm below the top frame by a wire. In addition to being placed on the swing, the rats were exposed to constant dedicated air flow directed at the face.

While riding the swing, blinking rates in rats were markedly reduced by approximately 30% compared with that during a normal state. This decrease in blink frequency upon swing-riding was accompanied by a decrease in tear fluorescein

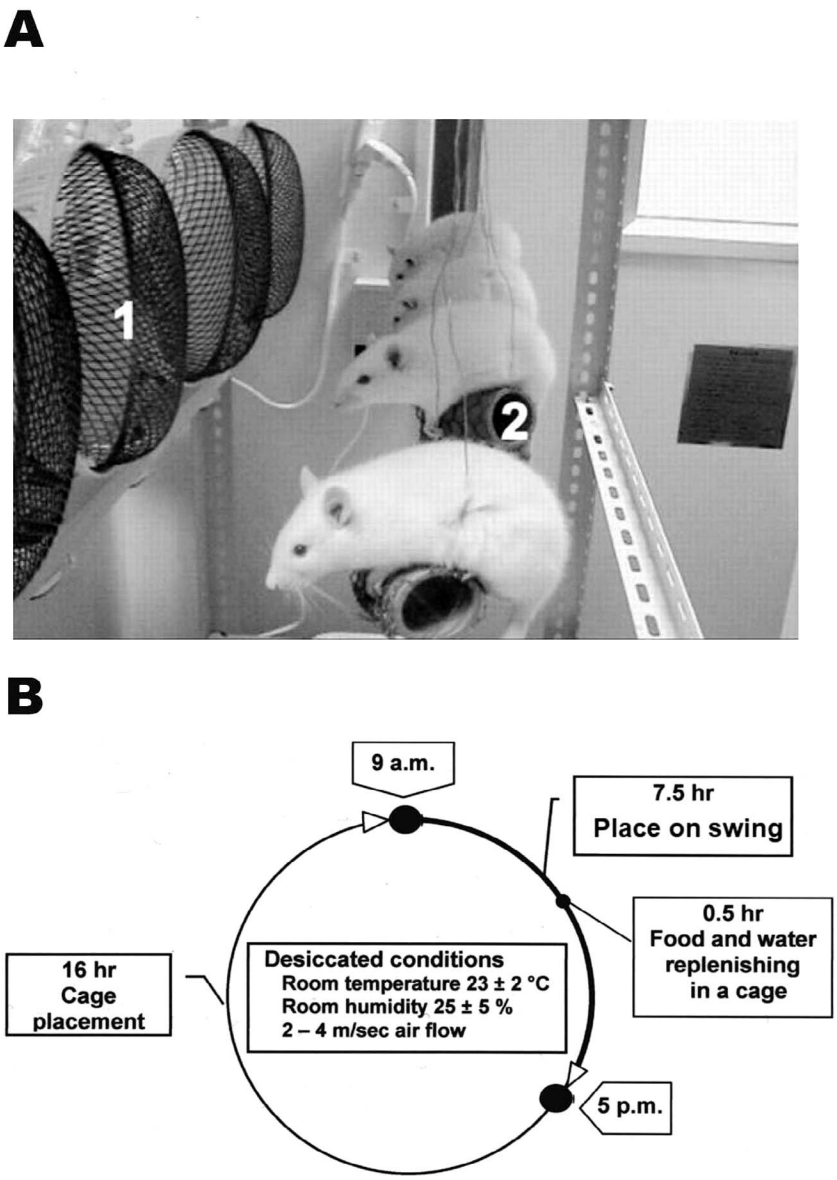


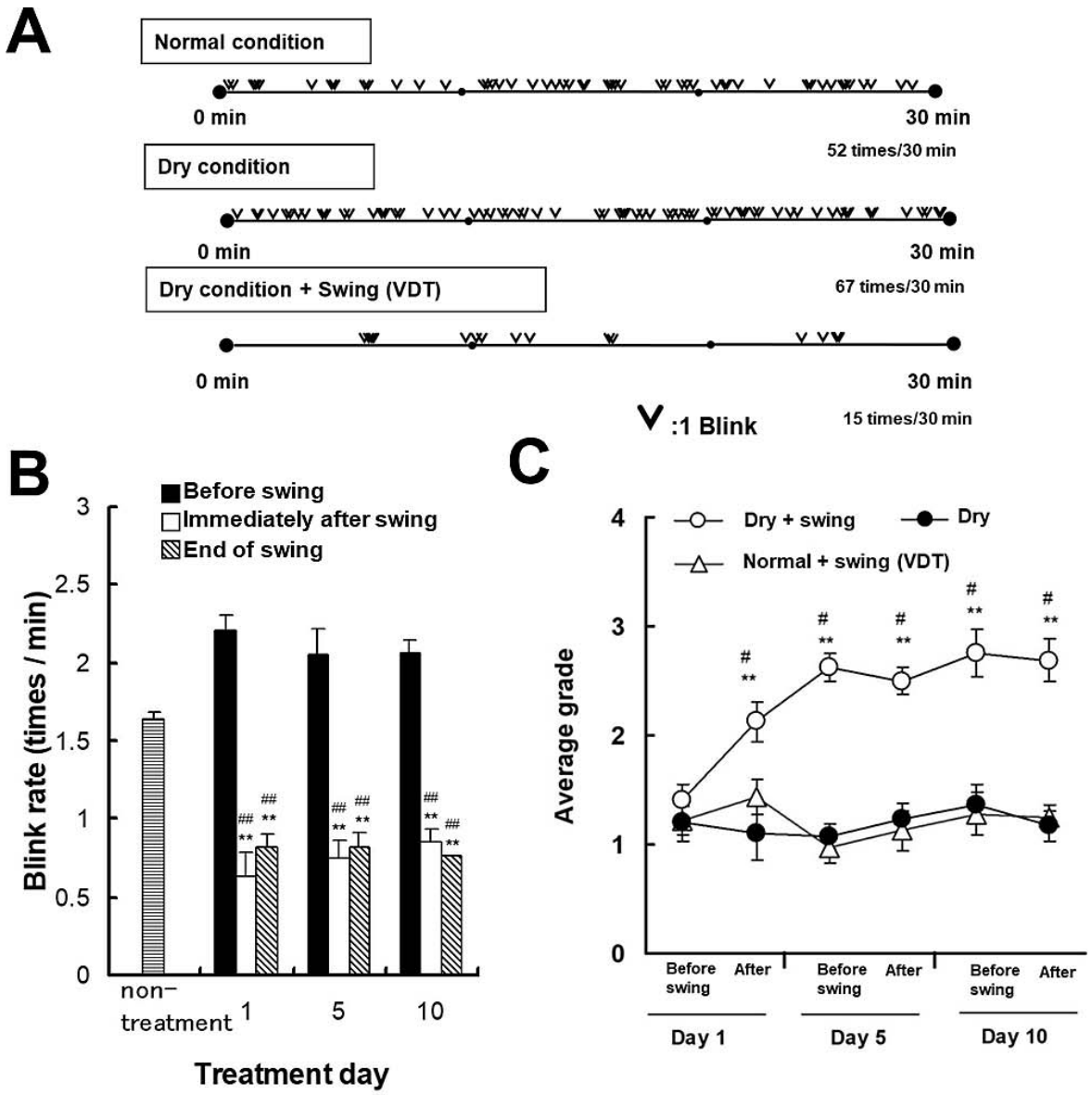
FIGURE 1. Rat–VDT user dry eye model. (**A**) Photograph of dry eye treatment. (*1*) Electric fan, (*2*) swing. (**B**) Schematic representation of the daily experimental schedule.

clearance, which indicated a reduction of the tear discharge rate by low blink frequency (Figs. 2A, 2B). In addition, mild corneal epitheliopathy was induced chronically (Figs. 2C–E). It has been reported that human blink frequency suppresses to approximately 20% during VDT work compared with non-VDT work.

The ocular surface is strongly affected by oxidative stress, which causes the corneal, conjunctival injury.[14] An increase in reactive oxygen species (ROS) and oxidative stress have been identified in the ocular surface of dry-eye patients and animal models.[15] In the rat–VDT worker dry eye model, the increase in the relative expressions of antioxidant genes SOD1, catalase, and glutathione peroxidase were accompanied by an increase in the proinflammatory cytokine matrix metalloproteinases (Figs. 3A, 3B).[16] In addition, ROS formation, the levels of damaged DNA, and the protein modification by reactive aldehydes in the corneal epithelia were significantly increased (Fig. 3C). Together, it can be assumed that this dry eye model mimics the condition of VDT work and is a useful tool to investigate the underlying mechanism, as well as to develop novel treatment approaches for network-mediated communication-associated dry eye.

LACRIMAL HYPOFUNCTION INVOLVED IN ETIOLOGY OF VDT USE–RELATED DRY EYE

A cross-sectional epidemiologic study of Japanese office workers (n = 1025) showed that there was a positive relationship between the duration of work in yearly and daily usage of VDT and a decrease in Schirmer values.[17] This indicates that the duration of VDT use has an etiologic association with a decrease in tear secretion. In the rat–VDT worker dry eye model, chronic decreases in blink frequency and an appearance of corneal epitheliopathy were accompanied with persistent decreases in tear secretion (Fig. 4A). In addition, corresponding to the human study, the reduction of tear secretion depended on strain duration (Fig. 4B).[17]



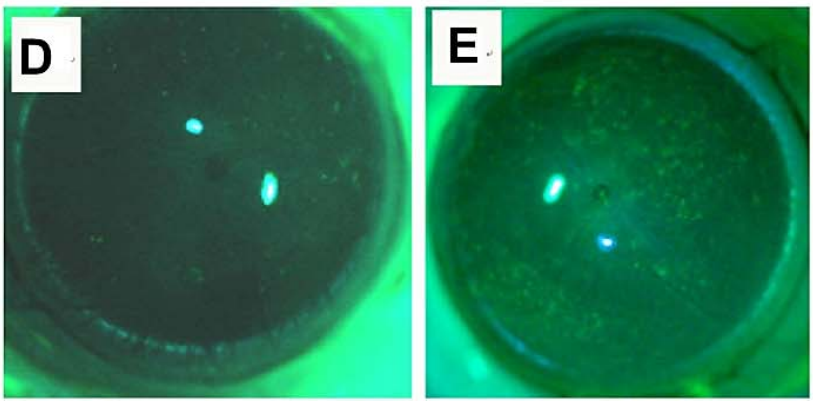


FIGURE 2. A reduction in blink frequency and increased corneal epitheliopathy were revealed in this rat–VDT worker dry eye model. (**A**) Typical blinking pattern of rat during 30 minutes in normal condition, dry condition, and dry + swing. The cephalic region of each rat was continuously monitored for 30 minutes from a horizontal angle with a digital video recorder, and the blink rate was counted by analysis of the video images. (**B**) Changes in blink frequency during dry eye treatment. The data represent the mean ± SE of four rats. $^{*}P < 0.05$, $^{**}P < 0.01$ versus the nontreatment group; $\#P < 0.05$, $^{\#\#}P < 0.01$ versus before treatment on the corresponding day by the Dunnett test. (**C**) Changes in the corneal fluorescein score during dry eye treatment. The data represent the mean ± SE of results in 16 eyes. $^{*}P < 0.01$ versus the dry condition and normal condition + swing group; $\#P < 0.05$ versus before treatment on day 1 by the Steel test. (**D**) Typical initial pattern and (**E**) in the same eye after 5 days of treatment dry + swing.

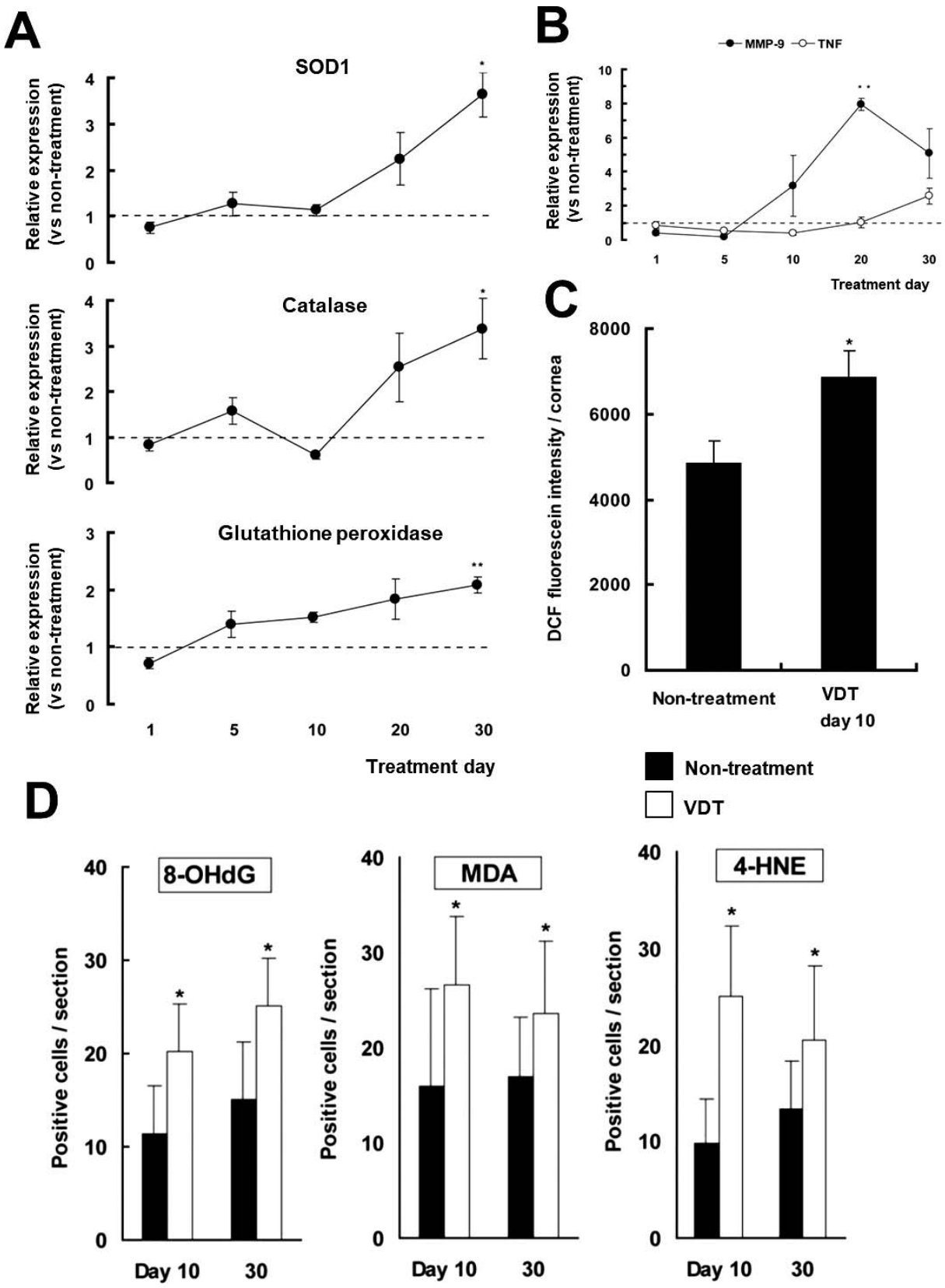


FIGURE 3. Involvement of oxidative stress on the ocular surface of the rat–VDT worker dry eye model. (**A**) Changes in antioxidant-related gene expression in the corneal epithelia. Data represent the relative expression rate compared with the nontreated group rats. Data represent the mean ± SE of three measurements from 9 to 12 corneas. (**B**) Changes in proinflammatory cytokines-related genes, matrix metalloproteinase and TNF, and expression in the corneal epithelia. (**C**) Changes in ROS production in corneal epithelia after 10 days of dry eye treatment. Data represent the mean ± SE of 10 corneas. (**D**) Quantitative analysis of the expression of oxidative stress markers in the corneal epithelia in the rat–VDT worker dry eye model. 8-hydroxydeoxyguanosine (8-OHdG, *left*), malondialdehyde (MDA, *center*), and 4-hydroxynonenal (HNE, *right*). Each oxidative stress marker is immunohistochemically detected in corneal epithelia after 10 days of dry eye treatment. Data represent the mean ± SE of 16 corneas. $^{**}P < 0.01$, $^{*}P < 0.05$ versus the nontreatment group.

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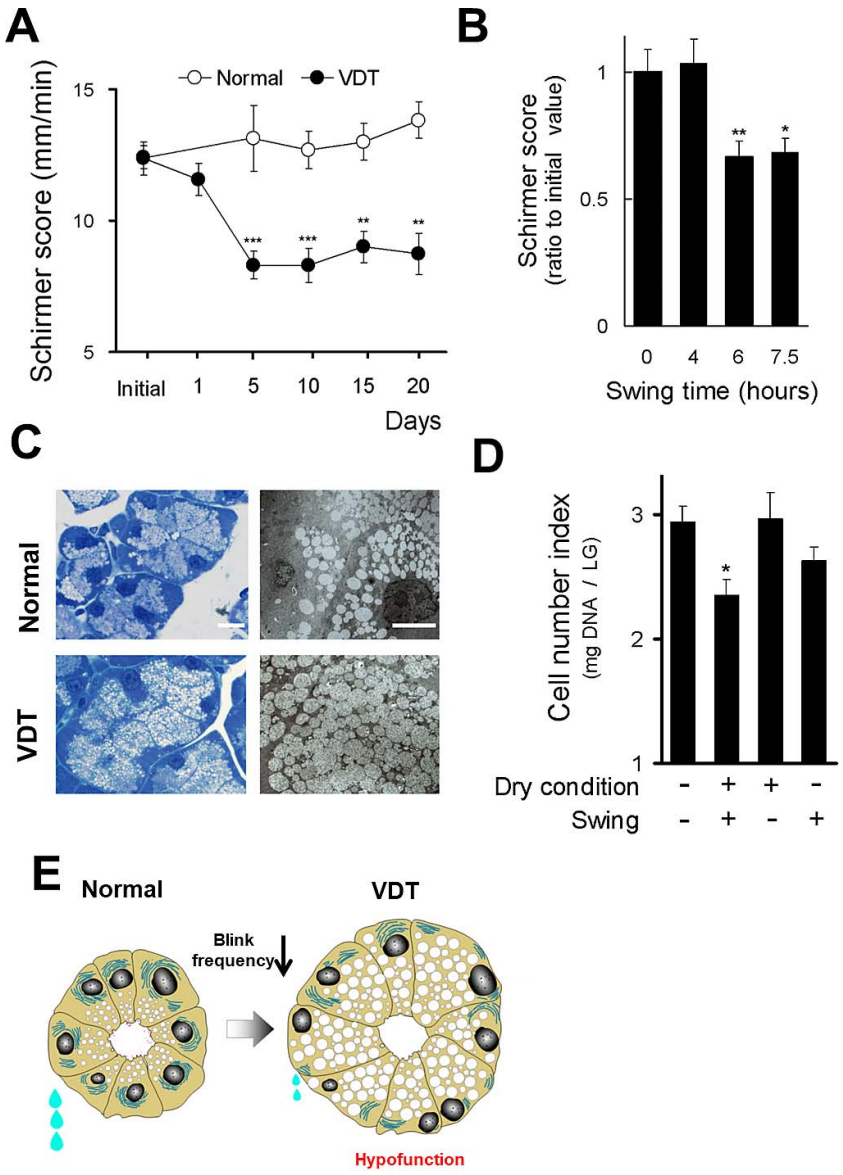

FIGURE 4. Lacrimal hypofunction in rat–VDT worker dry eye model. (**A**) Changes in tear production. Chronic reduction was observed during VDT. Data represent the mean ± SEM for 16 eyes. $^{**}P < 0.01$, $^{***}P < 0.001$ versus normal. (**B**) Effect of shortening the time spent on the swing. Ratios to initial value were calculated. Data represent the mean ± SEM for 16 eyes. $^{*}P < 0.05$, $^{**}P < 0.01$ versus 0-hour riding swing group. (**C**) Toluidine blue C staining right and left: Electron microscopic analysis of acinar cells. Images showing expanded acinar cells accompanied by accumulated enlarged secretory vesicle in the cytoplasm. (**D**) Changes in the total cell number of LG. Changes of LG cell number were measured 10 days after treatment with or without swing or dry condition. The quantification of LG number was calculated by DNA content of the LG. Data represent the mean ± SEM for 8 to 16 eyes. $^{*}P < 0.05$ versus the without swing and dry condition. (**E**) Schematic diagram of VDT-induced lacrimal hypofunction.

Aqueous tear fluid secretion from the LG is regulated by the sensory, sympathetic, and parasympathetic nervous systems. Basal tear secretion with continuous low-level flow is recognized as being maintained by a continuous neural stimulation to the LG, evoked from the corneal and conjunctival sensory nerves that are associated with blinking.[18] The pathologic analysis of LG in this dry eye model showed that the decrease in acinar cell number with an enlargement of acinar cells was accompanied by filling with an increased volume of secretory vesicles and the loss of intracellular cell structure (Figs. 4C, 4D).

These pathologic changes observed in the rats on the swing were characteristic of secretory dysfunction in other secretory glands, such as the salivary gland and pancreas, in which secretory mechanisms are analogous to those in the LG.[19,20] Furthermore, similar pathologic changes, such as the accumulation of secretory vesicles in the LG acinar cells, were noted in non-Sjögren's-type dry eye patients among VDT workers.[21] Based on these findings, it can be assumed that LG hypofunction contributes to the pathogenesis of VDT-associated dry eye (Fig. 4E). Because tear fluid secreted from the LG plays an essential role in maintaining a homeostatic environment for healthy ocular surface cells, dysfunction of the LG is similar as a pathologic situation involving the systemic circulation to likely promote heart failure.

MANAGEMENT FOR VDT-ASSOCIATED DRY EYE

The frequent application of viscoelastic artificial tear solution, wearing moist chamber spectacles, or lacrimal punctual

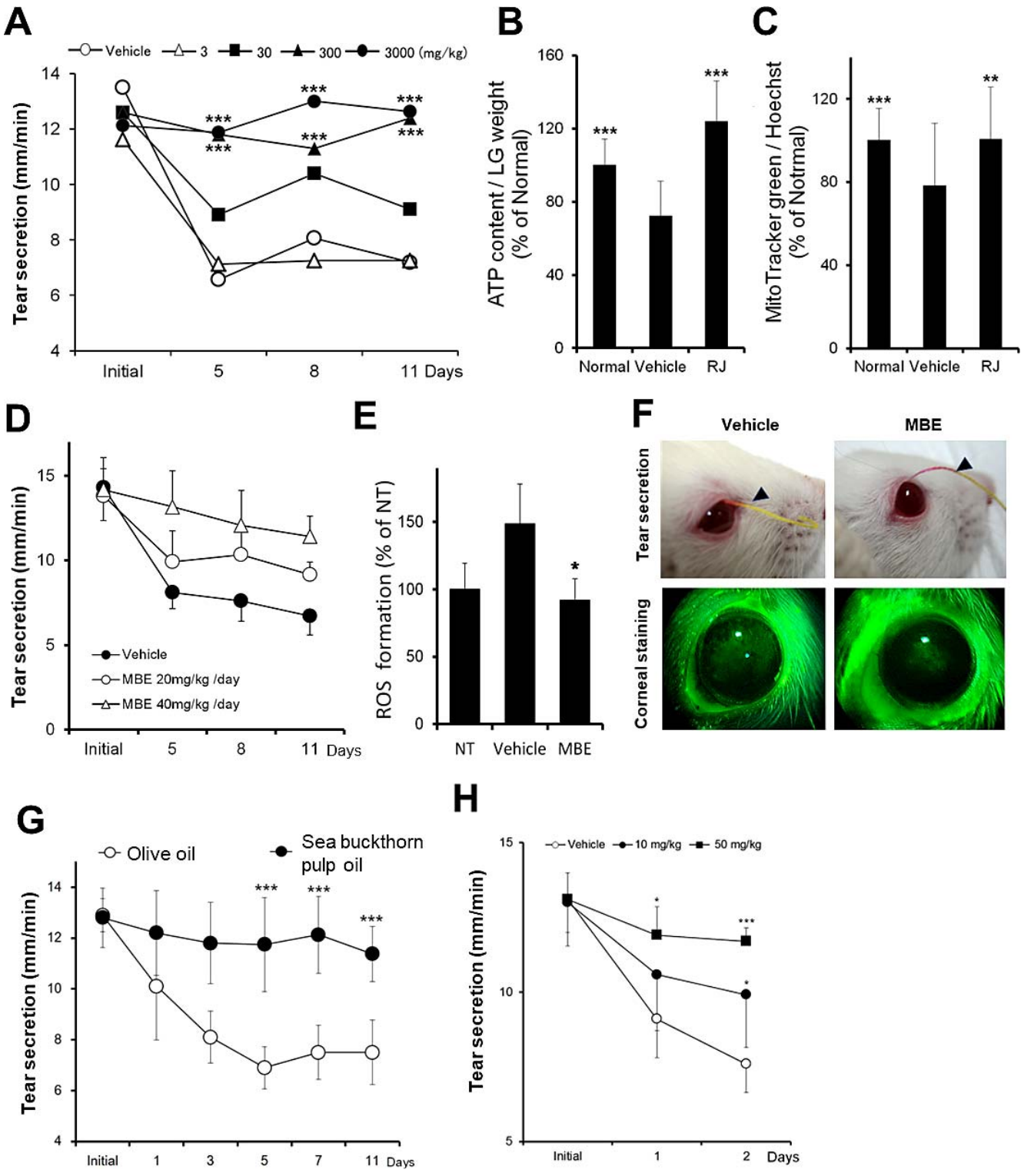

Figure 5. Management of lacrimal hypofunction by natural ingredients. Effect of oral administration of royal jelly on tear secretion (**A**), lacrimal gland ATP content (**B**), and lacrimal mitochondria content (**C**). Effect of Maqui berry extract on tear secretion (**D**), ROS formation in the LG from Maqui berry extract treatment (**E**). Typical tear secretion patterns measured by a cotton thread (*upper*) and corneal staining (*lower*) (**F**); punctate staining appeared in the whole corneal surface with the vehicle treatment. The *arrow* shows the wetted length by tear secretion. The effect of sea palmitoleate (C16:1) containing buckthorn oil on tear secretion (**G**). Effects of probiotics containing supplementation on tear secretion (**H**). Ingredients were evaluated using rat–VDT worker dry eye model. All data represent the mean ± SD. $^{**}P < 0.01$, $^{***}P < 0.001$ versus the vehicle.

occlusion by surgical or plug insertion treatment have long been considered basic management strategies for dry eye symptoms. However, these treatments are limited to the preservation of tear fluid to avoid dehydration in the ocular surface. The evidence from human epidemiologic studies and rat–VDT worker dry eye models suggest that the pharmacologic modulation of LG dysfunction may be a prospective treatment for VDT-associated dry eye. Therefore, the discovery and development of novel preventative interventions to maintain healthy LG function may be the focus of future work. Several interventional study groups have proposed to investigate the active agent for VDT-associated dry eye using this rat model.

Beekeeping products have been deeply rooted in the lives of different people and cultures worldwide for home consumption as food and as ingredients for healthy foods. Royal jelly, which the queen honeybee requires for its development, has been demonstrated to possess numerous biologic effects, such as antibacterial,[22] anti-inflammatory,[23] and hypotensive activities.[24] Ameliorative effects of orally applied royal jelly for dry eye symptoms by using the rat–VDT worker dry eye model demonstrated that royal jelly restored the tear secretion capacity (Fig. 5A). This effect along with an increase in ATP (Fig. 5B) and mitochondrial function (Fig. 5C) showed a preservation the energy status of LG, which is essential to maintain tear secretory processes and energy status for LG secretory function (Figs. 5B, 5C), which is essential to maintain tear secretory processes.[25]

Anthocyanins, natural water-soluble phenolic pigments of the flavonoid family, and rich berry extracts have been used as food supplements for the treatment of eye diseases based on their potent antioxidant properties.[26] Maqui berry (*Aristotelia chilensis*) extract originates from the berry grown in the Patagonia region of South America levees and has been used in traditional medicine for treating inflammation,[27,28] preserving the tear secretion capacity (Figs. 5D, 5F, upper), treating corneal epitheliopathy (Fig. 5F, lower), and suppressing ROS formation from LG tissue (Fig. 5E).[29] These effects are associated with the modulation of the LG secretory system through the suppression of oxidative stress stimulated by the Maqui berry, which has abundant delphinidin 3,5-O-diglucoside, an anthocyanin.

Polyunsaturated and saturated fatty acids have been recognized as essential nutrients for energy sources, vital structural components, and important cell signaling molecules with multiple biologic effects. The dietary intake of sea buckthorn, a shrub plant of the *Elaeagnaceae* family, which is widely grown in the central and northern areas of Eurasia berry oil, has been reported to attenuate the secretory function of tears in patients with dry eye syndrome.[30]

Using this dry eye model, researchers have compared the effect of sea buckthorn pulp oil on the restoration of tear secretion with that of olive oil, whose health benefits as a natural ingredient are well reported.[31] The superior effect of sea buckthorn oil compared with olive oil were noted, and this effect was possibly due to anti-inflammatory effects of palmitoleate (C16:1),[32] a fatty acid present in sea buckthorn pulp oil (Fig. 5F).

Probiotics are live microbial food supplements with beneficial effects on human health and have been used widely throughout history. A combined supplement with the probiotic *Enterococcus faecium* WB2000 may dose-dependently mitigate the decrease in tear production (Fig. 5G) and suppress ROS production from the LG.[33] These findings indicate that the oral supplementation of natural ingredients is a possible therapy for relieving symptoms of VDT-associated dry eye.

Additional clinical studies involving patients with dry eye, with VDT workers compared with adequate placebo controls are needed to prove the usefulness of these ingredients for the management of VDT-associated dry eye.

Further Direction of Basic Research on VDT

Dry eye symptoms are characterized by objective clinical signs and multiple subjective symptoms (burning, dry, and itching eyes).[34] Subjective symptoms are often exaggerated in office environments and have a great impact on quality of life.[35] It has been demonstrated that people working long hours with VDTs complain of a high level of ocular discomfort. Animal models of VDT-associated dry eye accompanied by ocular discomfort behavior have not been established because rodent behaviors corresponding to human dry eye–related ocular discomfort reactions are not fully identified. Ocular discomfort is induced by complicated sensory mechanisms involved in the activities of ocular surface sensation, local sensory nerve circuit, and higher central nervous system functions.[36] Investigations for the establishment of VDT use–associated dry eye models that may be used to evaluate ocular discomfort that mimic the condition in humans by using neuroscientific approaches may provide a straightforward strategy for understanding the underlying mechanisms and pharmacologic treatments for the restoration of VDT workers' dry eye.

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