

NS2, a novel aldehyde trap, decreases aldehyde levels in dry skin and eye models

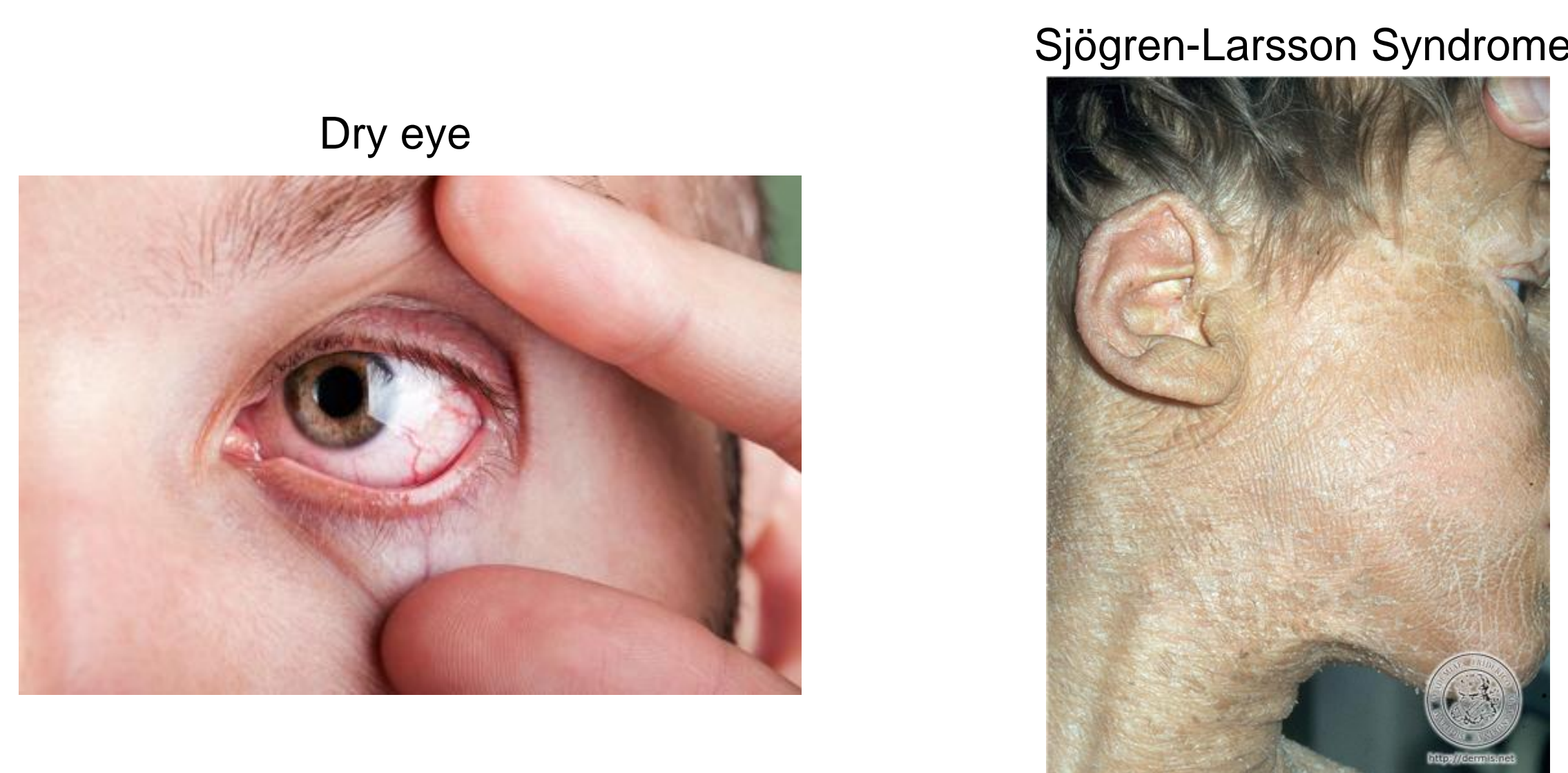
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Abstract

Free aldehydes are naturally occurring chemical species formed during a variety of biological processes, including polyamine and glucose metabolism and lipid peroxidation. Uncontrolled levels of aldehyde species can lead to inflammation via activation of the NF- κ B pathway and also damage key lipids that comprise the dermal moisture barrier and lubricate the surface of the eye. Elevated levels of malondialdehyde (MDA) have been shown in a variety of inflammatory skin and eye diseases, including psoriasis, atopic dermatitis, anterior uveitis, and rosacea. In addition, high levels of fatty aldehydes in Sjögren-Larsson Syndrome, an orphan disease caused by mutations in fatty acid aldehyde dehydrogenase, lead to severe ichthyosis, retinal disease and neurological disorders. Here, we report the effect of dry conditions on inducing MDA levels in human skin and eye tissue and the activity of NS2, a novel aldehyde-binding small molecule, in reducing levels of MDA generated by dry conditions. Topical application of NS2 cream to three-dimensional human skin equivalents lowered MDA levels (measured by TBARS assay) induced by dry skin conditions. Moreover, topical application of NS2 eye drops to three-dimensional human cornea-like tissue lowered MDA levels induced by dry eye conditions. These results suggest that NS2 could mitigate the toxic aldehyde load that is generated in dry skin and dry eye conditions. By trapping aldehydes, NS2 may protect skin and eye tissue from chronic inflammation caused by aldehydes that are generated in dry conditions, and in addition may protect lipids that are critical in preserving moisture in skin and eye. Thus, NS2 represents a potential novel compound that could provide a dual benefit to individuals with dry skin or dry eyes.

Fig 1. Dry skin and Dry eye conditions



Dry environmental conditions (high temperature, low humidity) can promote lipid oxidation and induce elevated levels of aldehyde species that may damage lipid-rich moisture barriers in skin and eye, generating further dryness. Deficiencies in aldehyde dehydrogenase activity in Sjögren-Larsson Syndrome, for example, may lead to high aldehyde levels and damage to the dermal moisture barrier that causes the severe ichthyosis characteristic of the disease. Since patients with dry eye syndrome manifest elevated aldehyde levels in tears, aldehydes may also compromise the moisture barrier in the eye and thereby exacerbate dryness. Thus, lowering aldehyde levels may represent a novel therapeutic approach for treating dry skin and eye conditions.

Fig 2. NS2: A novel aldehyde trap

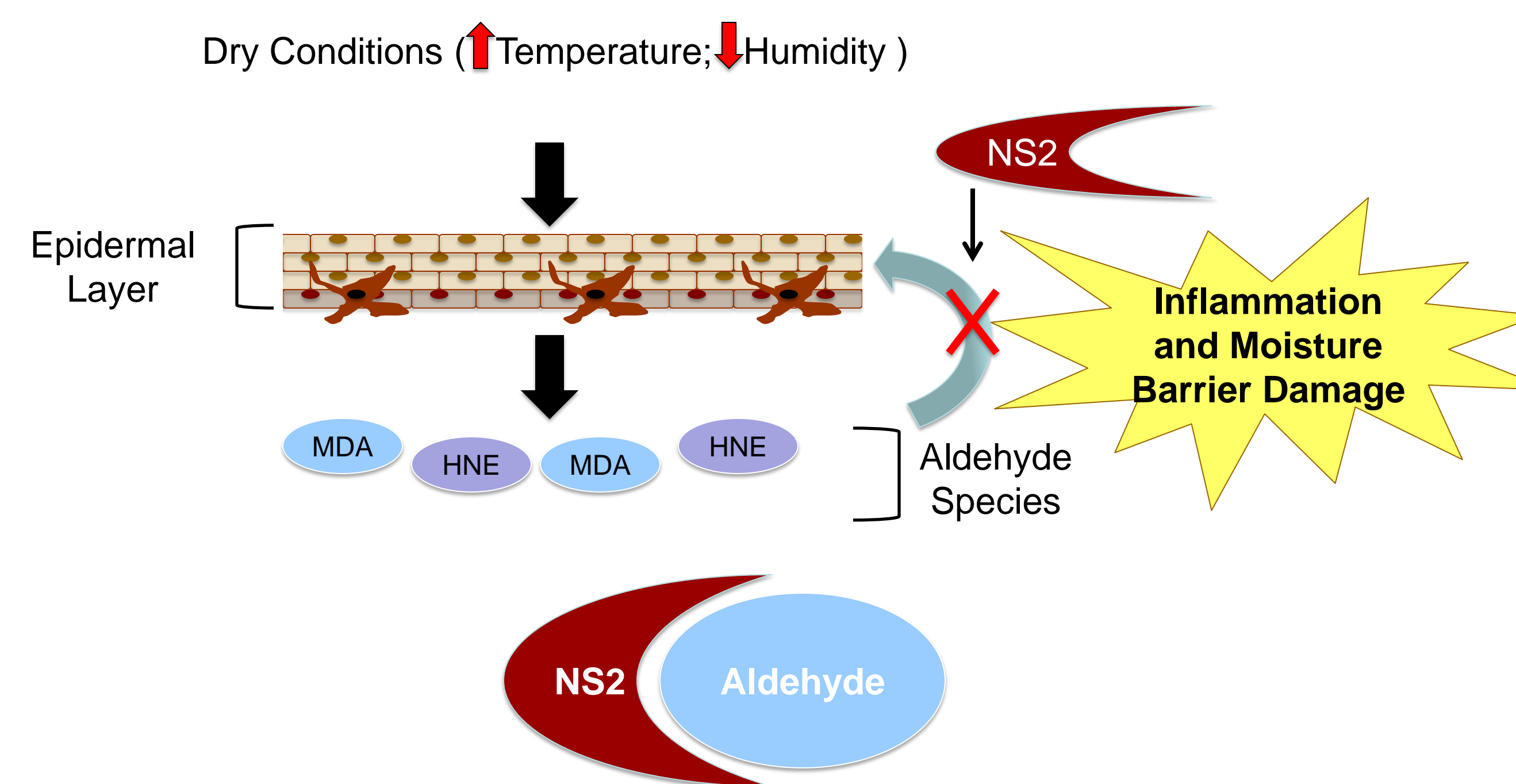
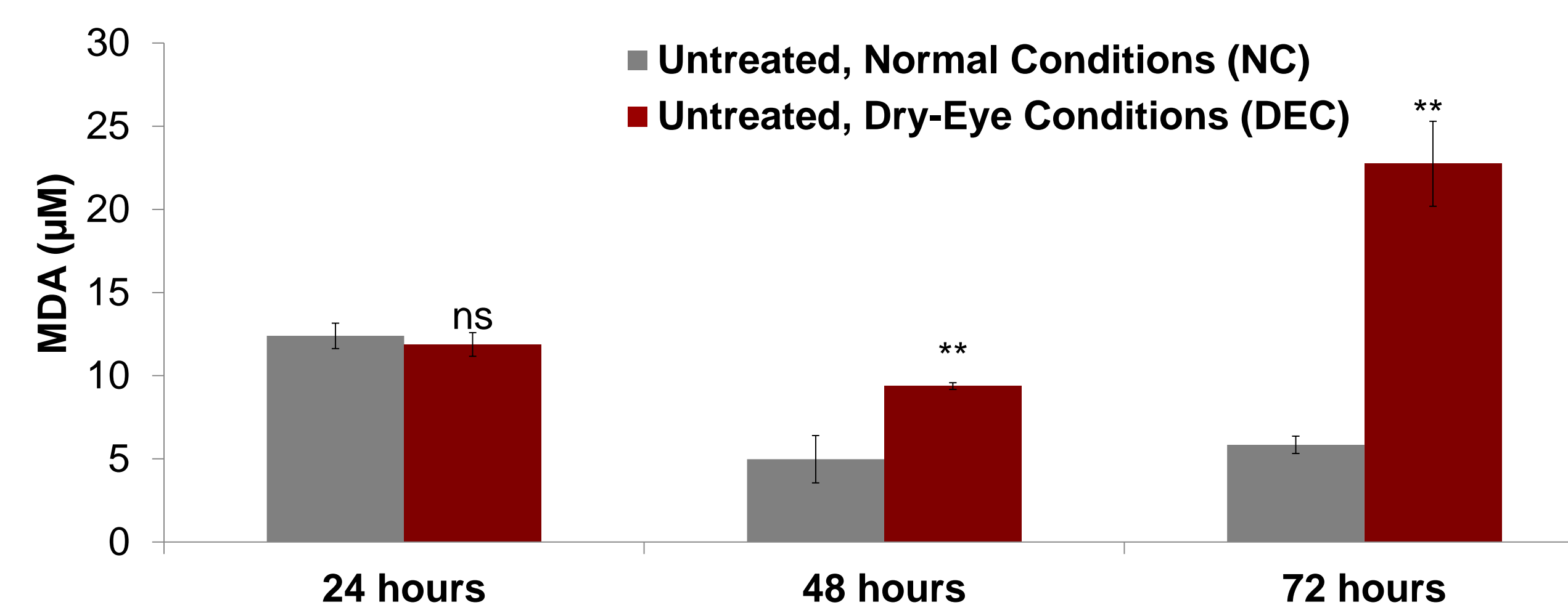
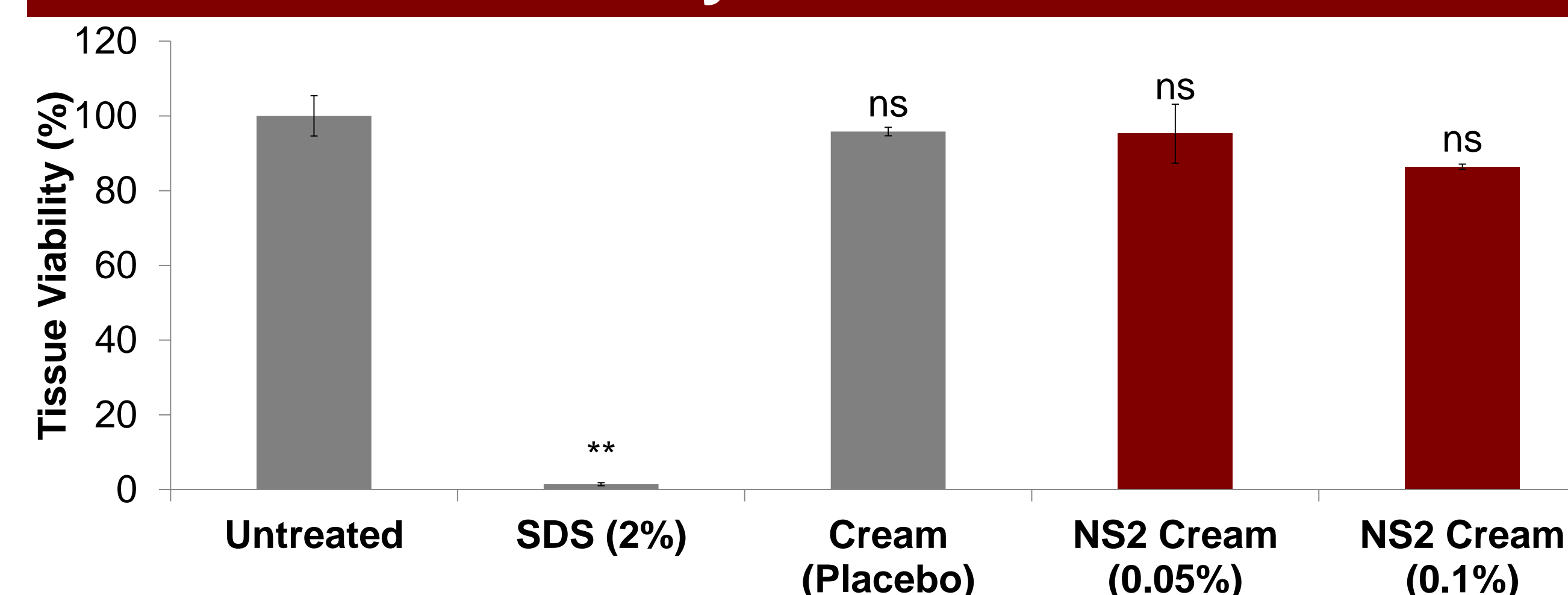


Fig 3. Dry conditions increase aldehyde levels in human tissue



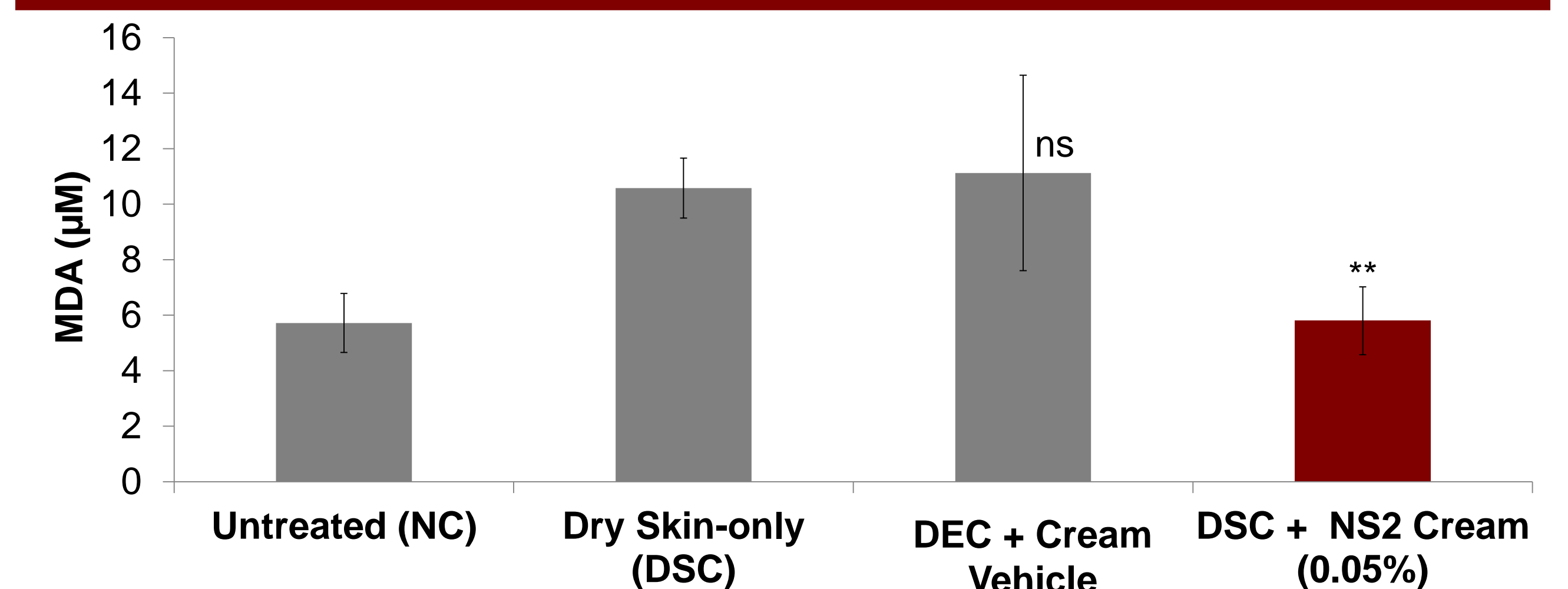
EpiOcular™ (MatTek®) tissues were acclimated before treatments for 24 hours and then incubated under normal (37° C; >40%RH) or dry-conditions (40° C; <40%RH) for 24, 48 and 72 hours. Malondialdehyde (MDA) levels of tissue lysates were measured using the TBARS assay. (ns = non significant; ** = p<0.01)

Fig 4. NS2 cream formulations do not affect viability of 3D skin models



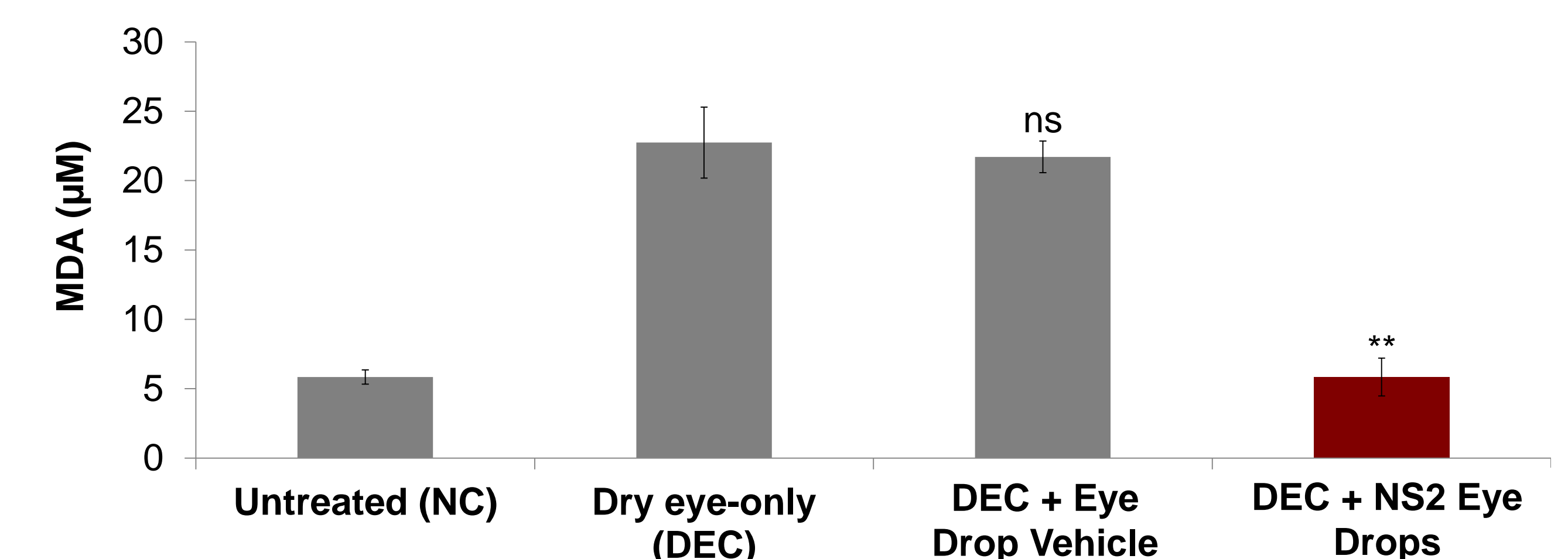
NS2 cream formulations were tested for skin irritation in reconstructed human epidermis. EpiDerm™ (MatTek®) tissues were acclimated for 24 hours and then treated topically twice (12 hours apart) with NS2 cream formulations (0.05% and 0.1% w/v) or SDS (2% w/v), used as positive control. Tissue viability levels were measured by the MTT reduction assay 48 hours after treatments. The levels of tissue viability after each treatment were compared to the untreated group to estimate the potential for skin irritation. (** = p<0.01)

Fig 5. NS2 prevents the increase in aldehyde levels caused by dry conditions in skin tissue



In a topical dermatologic formulation, NS2 (0.05% w/v) was administered to reconstructed human epidermis under normal and dry skin conditions (DSC). EpiDerm™ (MatTek®) tissues were acclimated before treatments for 24 hours and then treated topically with or without NS2. Tissues were incubated under normal (37° C; >40%RH) or DSC (40° C; <40%RH) for 72 hours. Malondialdehyde (MDA) levels of tissue lysates were measured using the TBARS assay and compared to untreated tissue. (** = p<0.01).

Fig 6. NS2 prevents the increase in aldehyde levels caused by dry conditions in ocular tissue



In an eye drop formulation, NS2 (0.5% w/v) was administered to reconstructed human cornea-like tissue under normal and dry eye conditions (DEC). EpiOcular™ (MatTek®) tissues were acclimated before treatments for 24 hours and later treated topically with or without NS2. Tissues were incubated under normal (37° C; >40%RH) or DEC (40° C; <40%RH) for 72 hours. Malondialdehyde (MDA) levels of tissue lysates were measured using the TBARS assay and compared to untreated tissue. (** = p<0.01).

Summary/Conclusions

- ✦ Dry conditions induce aldehyde generation in human dermal and ocular tissue.
- ✦ Cream placebo used for NS2 active formulations and NS2 creams between 0.05-0.1% are unlikely skin irritants when topically applied twice a day (12 hours between application).
- ✦ In topical dermatologic and eye drop formulations, NS2 has significant aldehyde trapping activity in human dermal and ocular tissue subjected to dry conditions.
- ✦ Topically applied NS2 could be a safe and effective treatment for diseases characterized by dry tissue.