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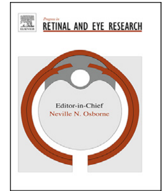

Clinical staining of the ocular surface: Mechanisms and interpretations

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A B S T R A C T

In this article we review the mechanism of ocular surface staining. Water-soluble dyes are excluded from the normal epithelium by tight junctions, the plasma membranes and the surface glycocalyx. Shed cells can take up dye. A proportion of normal corneas show sparse, scattered time-dependent, punctate fluorescein uptake, which, we hypothesise, is due to a graded loss of the glycocalyx barrier, permitting transcellular entry into pre-shed cells. In pathological staining, there is little evidence of 'micropooling' at sites of shedding and the term 'punctate erosion' may be a misnomer. It is more likely that the initial event involves transcellular dye entry and, in addition, diffusion across defective tight junctions. Different dye-staining characteristics probably reflect differences in molecular size and other physical properties of each dye, coupled with differences in visibility under the conditions of illumination used. This is most relevant to the rapid epithelial spread of fluorescein from sites of punctate staining, compared to the apparent confinement of dyes to staining cells with dyes such as lissamine green and rose bengal. We assume that fluorescein, with its lower molecular weight, spreads initially by a paracellular route and then by transcellular diffusion. Solution-Induced Corneal Staining (SICS), related to the use of certain contact lens care solutions, may have a different basis, involving the non-pathological uptake of cationic preservatives, such as biguanides, into epithelial membranes and secondary binding of the fluorescein anion. It is transient and may not imply corneal toxicity. Understanding the mechanism of staining is relevant to the standardisation of grading, to monitoring disease and to the conduct of clinical trials.

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1. Introduction

Topical dyes are used extensively to characterize ocular surface diseases and quantify their severity. The distribution of micropunctate staining may provide an etiological clue.

The most frequently used dyes are disodium fluorescein, lissamine green and rose bengal, although mixtures of dyes have also been used (Norn, 1962, 1965, 1967, 1972; Toda and Tsubota 1993; Chodosh et al., 1994; Korb et al., 2008; Yoon et al., 2011), including a triple dye mixture containing alcian blue (Norn, 1964).

There has been a longstanding debate as to the mechanism of staining by these dyes, which is relevant not only to the pathophysiology that they help to reveal, but also to the standardization of grading in clinical practice. In this review we will use the term 'punctate staining' in a general sense, to refer to punctate spots of dye at the surface of the epithelium, whether or not they are taken up into cells. Various possible mechanisms will be discussed, and in order to understand them it is important to consider those aspects of the corneal and conjunctival epithelia that influence dye behaviour.

2. Anatomical and physiological factors affecting staining

2.1. General aspects

The *corneal epithelium* is a 5 layered structure possessing a basal layer of columnar cells, about 10 μm wide, intermediate layers of wing-shaped cells and a superficial layer of large, flat, polygonal cells, about 35 μm in diameter (Lemp and Mathers, 1989).

These most superficial cells are connected to one another by intercellular *tight junctions* (*zonulae occludentae*) that encircle each cell and to an important extent obliterate the intervening paracellular space (Fig. 1). They thus retard the passage of ions and of hydrophilic molecules above a certain size, from the tears into the epithelium. Functionally, these junctions are sufficiently tight to convert this layer into an almost perfect semipermeable membrane towards sodium (Maurice, 1969), but are sufficiently leaky to allow the permeation of small hydrophilic molecules.

2.2. Tight junctions

The tight junctions (Tjs) of the corneal epithelium consist of the trans-membrane proteins occludin, claudin and the junctional adhesion molecules (JAM), and the peripheral membrane proteins, ZO-1,-2 and -3 and MUPP-1 (Tsukita et al., 2001; Ban et al., 2003a, b). Other cytoplasmic proteins, such as cingulin and 7H6 antigen, are also present (Tsukita et al., 2001). Their organisation has been summarised by Ban et al. (2003a, b). Occludins and claudins contain 4 transmembrane domains, with both their N- and C-termini directed towards the cytoplasm. Occludin combines with tissue-specific members of the claudin family to form paired strands, one from each adjacent cell, that cross between the cells and close the intercellular space (Furuse et al., 2002). Occludin functions as a regulatory protein controlled by phosphorylation and has no significant structural role (Furuse et al., 1993). It may have permeability-related functions (Yu et al., 2005) and influence cell division (Wang et al., 2005).

The ZO (zonula occludens) proteins are members of the Membrane-Associated Guanylate Kinase (MAGUK) proteins and are

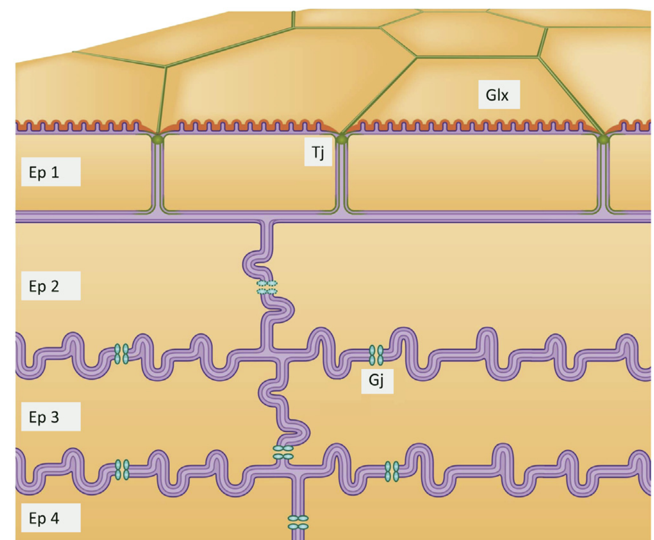

Fig. 1. Diagram of the human corneal epithelium to show components which influence permeability. The glycocalyx of the surface epithelial cells is shown in pink (Glx). Tight junctions (Tj – in green) retard the entry of water-soluble molecules into the paracellular spaces. Functional gap junctions (Gj) are not present in the most superficial epithelial layer (layer 1) and are of limited functionality in the second layer (dotted channels). Gap junctions are fully functional in the third and deeper layers (continuous lines). Desmosomal attachments are not shown (See text for details).

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