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Review

Effects of mechanical forces and stretch on intercellular gap junction coupling ☆

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ABSTRACT

Mechanical forces provide fundamental physiological stimulus in living organisms. Recent investigations demonstrated how various types of mechanical load, like strain, pressure, shear stress, or cyclic stretch can affect cell biology and gap junction intercellular communication (GJIC). Depending on the cell type, the type of mechanical load and on strength and duration of application, these forces can induce hypertrophic processes and modulate the expression and function of certain connexins such as Cx43, while others such as Cx37 or Cx40 are reported to be less mechanosensitive. In particular, not only expression but also subcellular localization of Cx43 is altered in cardiomyocytes submitted to cyclic mechanical stretch resulting in the typical elongated cell shape with an accentuation of Cx43 at the cell poles. In the heart both cardiomyocytes and fibroblasts can alter their GJIC in response to mechanical load. In the vasculature both endothelial cells and smooth muscle cells are subject to strain and cyclic stretch resulting from the pulsatile flow. In addition, vascular endothelial cells are mainly affected by shear stress resulting from the blood flow parallel to their surface. These mechanical forces lead to a regulation of GJIC in vascular tissue. In bones, osteocytes and osteoblasts are coupled via gap junctions, which also react to mechanical forces. Since gap junctions are involved in regulation of cell growth and differentiation, the mechanosensitivity of the regulation of these channels might open new perspectives to explain how cells can respond to mechanical load, and how stretch induces self-organization of a cell layer which might have implications for embryology and the development of organs. This article is part of a Special Issue entitled: The Communicating junctions, roles and dysfunctions.

Contents

1. Stretch, stress, strain, etc.: the physical definitions

Life of mammalian organisms involves movement in many respects: movement of the organism in the landscape or generally in space, but also the movement of blood in the cardiovascular system that keeps the organism alive. All movement exerts an interaction

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between the moving medium and the surrounding. This will result in e.g. pressure, strain, stretch, shear stress, or friction or combinations of these. Typical physiological changes related to these phenomena occur in the heart and the vessels. The contraction of the heart imposes pressure on the heart walls. Thus, the investigation of the effects of mechanical load on cells is an important topic for research. Since the processes involved in adaption to mechanical load also include growth and differentiation, and since these two are also affected by gap junctional intercellular communication, the effect of mechanical load on gap junctions has become a new interesting field in gap junction and biomechanical research. Before pointing out the present views on these effects, it is necessary to give some definitions. Mechanical load can mean simply pressure, or cyclic or static stretch, or strain, or in some models shear stress (Fig. 1). Since these terms are often used loosely, they shall be defined here at the beginning more precisely to discriminate between the processes.

Pressure (P) normally is defined by physicists as force (F) per unit area (A) in the direction normal to the surface (Fig. 1):

$$P = F/A$$

This force, which may be pressure or traction force, may lead to a deformation of the body to which surface this force was applied to. In case of traction the body will be elongated in the direction of force, in case of pressure it will be compressed and shortened in direction of the force. This change in length (Δl) in direction of the stretch related to the initial length (l) ($\Delta l/l$) is named stretch (ε) (dimensionless) (Fig. 1) and can be described as

$$\varepsilon = \Delta l/l$$

which will depend on the force (F) in direction of stretch and on the area of transverse section (A) so that

$$\sigma = F/A$$

and

$$\Delta l/l = l/E * \sigma$$

or combining these formulas stretch of a body with the transverse section area A can be described by Hooke's law (Fig. 1) as

$$\varepsilon = (1/E) * \sigma$$

with E being the elasticity modulus [a material constant given in $[N/m^2]$. The tension applied to the transverse section of the body can be described as normal stress $[N/m^2]$ (σ).

Mostly, it is more interesting in biomechanics or in physiology to regard the change in extension or change in length, i.e. the stretch ratio (λ), which is defined by the ratio between the final length (ℓ) (not the increment Δl as above) and the initial length (L):

$$\lambda = \ell/L$$

Sometimes, it may be more interesting to regard the extension ratio (e) which is

$$e = (\ell - L)/L$$

or in other words: $e = \lambda - 1$ which implies that the normal strain is zero and that under normal condition there is no deformation if stretch is zero.

In case of such a deformation an inverse change Δd will occur 90° to the stretch axis. The ratio between length change in stretch axis (Δl) and transverse to it (Δd) is called Poisson's number (μ), which is a material constant

$$\mu = (\Delta d/d) : (\Delta l/l)$$

which varies for most materials between 0.2 and 0.5. As a consequence of this, a slight change in volume may occur, which according to Hooke's law can be described as

$$\Delta V/V = 1/E\sigma * (1 - 2\,\mu)$$

with σ being the normal stress $[N/m^2]$.

For a normalized measure of deformation physiologists often use the general term strain (ζ) (Fig. 1) representing the displacement

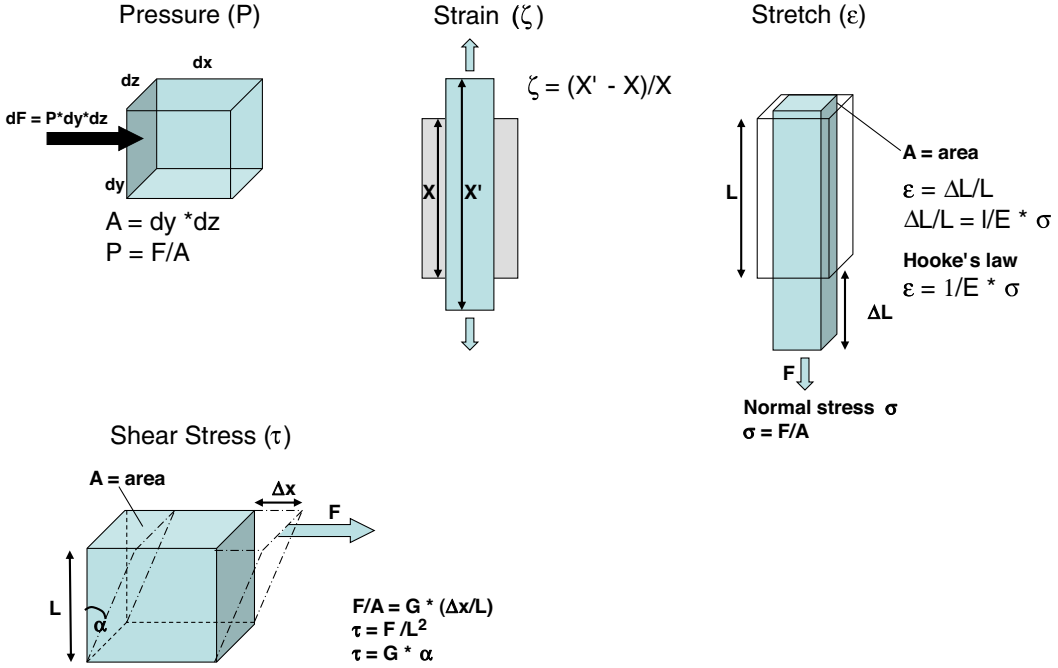

Fig. 1. Scheme of some of the mechanical forces as discussed here. Abbreviations and symbols are according to the explanations in the text (see first section on the physical definitions).