Mechanosensitive Ion Channels

Senses supply the necessary information to construct the human made image of the world and universe. Philosophically, perception of the world is limited mainly by the variance of the sensory information. The subject has been so interesting that it has attracted many philosophers and scientists since the ancient times. Touch, which is based on mechanosensation, is perhaps the most ancient one among all the senses as Aristotle has mentioned about the importance of the tactile sensation for humans in his book De Anima III many centuries ago. Considering the phylogenetic point of view, mechanosensation is present in all the species ranging from bacteria to mammalians. For example: A Mechanosensitive (MS) ionic current or ion channels has been reported in bacteria wall [1], paramecium membrane [2], and vertebrate [3] and mammalian [4] cells. The principle component of the mechanosensation is a distinct type of transducer ion channel, opening (or closing) in response to a mechanical deformation of the cell membrane, the mechanosensitive ion channel. MS ion channels constitute another class of ion channels in addition to the voltage and agonist gated channels. In humans (or mammalians) it has been reported that MS channels are involved in several important physiologic functions such as sensation of tactile stimulus, pain, hearing, proprioception, synaptogenesis, regulation of cell volume and heart rate [5-9]. Further, dysfunction of the MS ion channels has been associated to various disease states like arrhythmia, pulmonary hypertension, muscular dystrophy, polycystic kidney disease, mechanical allodynia, anemia, peripheral paresthesia, tumor metastasis [10-17].

Presently, molecular properties of the voltage or agonist gated channels has been well documented in many species and the number of the family members are above 400 in humans. However, very few information is available about the molecular properties of the MS ion channels in contrast to the physiological relevance and homogeneous distribution among the species. The only available information related to the molecular properties of the MS channels is solely confined to those in bacteria wall and some invertebrate sensory neurons [18-20]. Thus, it is apparent that molecular properties of the MS ion channel and a component of mechanotransduction process has not been comprehensively investigated yet.

The research in the area moves slowly due to several factors, discussed in the following section. Mechanosensation might have evolved differently in various body parts. Thus, mechanotransduction components in the skin touch receptors and hair cells of the inner ear would not be the same. Thus, a substantial amount of variance is expected in the molecular properties of MS channels within those structures, evolved to transduce the mechanical force into a different sensory modalities. Majority of the functional studies, related to the MS channels, are based on recording of the electrical responses to a form of mechanical stimulation [3,4,21-25] or blockage of the responses by some chemicals [26,27]. Keeping the stability of the recording configuration is a major problem during the mechanical stimulations. Thus, those kind of functional experiments are extremely difficult to conduct at the cellular and subcellular level. Further, presence of any form of mechanosensation capacity alone would not be a reliable indicator of a MS channel. Recent, reports indicates that a large group of voltage or agonist gated ion channels are also mechanosensitive. Nav1.5 [28], Nav1.6 [29], Cav1.2 [30], Kv1 [31], Kv7 [32], KATP [33], DEG/ENaC [34], TREK-1 [35], TRAAK [36], TRP [37-39], NMDA [41], CFTR [42] and TMC [43] channels may respond to a mechanical stimulation. By a careful inspection of the published results it might be proposed that sufficiently convincing data may be available only for TMC, TRP, DEG/ENaC channels. In addition to those multimodal channels, MscS channels of the bacteria wall and Piezo channels, firstly described in invertebrates and then mammalians, are the two mechanosensitive ion channels available at present [44,45]. It is apparent that a large group of ion channel has been associated to mechanotransduction process. However, the molecular structure of those channels are extremely heterogeneous. Neither structural architecture nor the amino acid sequences of any of those channels are similar. Further, physiological functions, pharmacological properties and the gating machinery of the MS channels differ substantially. For example MscL, TRAAK, NMDA, CFTR...
Piezo1 type channels can be blocked by ruthenium red or more specifically by Grammasutola Toxin (GT) [46-49]. It has been proposed that GT blocks the MS channel by changing the profile of the lipid bilayer as documented in the gating mechanism of TRAAK channel [48] where at resting state lipid chains shown to block the ion passage by filling the channel pore. Mechanical deformation removes the lipid chains and moves the channel to a conducting state. GT interferes with the lipid bilayer so that mechanical stimulus fail to remove the lipid chains from the channel pore. Such a gating mechanism is defined as the “bilayer model”. However, GT fails to block all kinds of mechanosensitive channels or currents indicating that the lipid bilayer model would not be the only gating mechanism. In hair cells of inner ear different types of structural proteins like actin, protocadherin, ankyrin are necessary to activate the MS current (i.e. MS channel) [50]. MS current could not be initiated when any of those proteins are eliminated. Unlike the previous model in hair cell MS channel should be attached to cytoskeleton or intercellular matrix by those proteins. The model is called “tethered model” [50-52]. Apparently, in the tethered model instead of a single ion channel molecule we should be dealing with a “mechanosensitive ion channel complex”, consisted of structural proteins and channel molecule in a certain configuration to convert mechanical force into ionic current.

It is evident that putative MS channels differ substantially with refer to gating and pharmacological properties. In order to contrast the degree of variance; we may recall that the whole voltage gated ion channel family might have reportedly been evolved from a single primordial member and the molecular architecture of the whole group could be assigned into four basic models [53,54]. None of those properties are relevant for MS channels. Presently, in contrast to the extensive research in the area molecular properties of only bacterial MS channel and Piezo channels are known. Bacterial channels are not present in humans and Piezo 2 is reported only in epidermal Merkell cells [55]. Further, mutations in piezo1 and piezo2 genes caused hereditary xerocytosis and loss of proprioception in humans, respectively [56]. Though, Piezo channels seems as the most promising candidate member for MS channel family, however fails to cover the entire physiological functions based on MS ion channels or channel complex, ranging from sensation of tactile stimulus to hearing.

MS properties of rest of the channels, already discussed above, might be a matter of debate. For example TMC channel has been proposed as the MS transducer channel in the hair cells since a certain form of deafness is observed in individuals having mutations in the related gene [57]. The theory has been supported by the observation that the transducer current is not present in the knock out animals when the hair cell were stretched towards the direction of activation [58]. However, in another study it was reported that the transducer current could be observed in knock out animals if mechanical stimulus was applied in the direction of inactivation [59].

As it is discussed in this short editorial article MS channel or channel complex is perhaps the most complicated transducer channel group with respect to physiological, pharmacological and structural properties. Though, many candidates has been proposed a lot more information is required to explore the molecular basis of mechanotransduction.

References