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Journal Club

Upregulation of $Na_v1.7$ Through High Salt Loading

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Summary

The role of $Na_v1.7$ in electrogenesis in dorsal root ganglion (DRG) and sympathetic ganglion neurons is well-established, and it is clear that $Na_v1.7$ functions as a threshold channel in these neurons, amplifying small depolarizing inputs to bring the cell to threshold for action potential generation and facilitating neural transmitter release.[1-3] $Na_v1.7$ dysfunction is associated with different human pain disorders. Gain-of-function missense mutations in $Na_v1.7$ have been shown to cause primary erythermalgia and paroxysmal extreme pain disorder,[4-7] while nonsense mutations in $Na_v1.7$ result in loss of $Na_v1.7$ function and a condition known as channelopathy-associated insensitivity to pain, a rare disorder in which affected individuals are unable to feel physical pain.[8-11]

A number of mediators, including prostaglandin,[12] adenosine[13] and serotonin,[14] affect the electrophysiological properties of voltage-gated sodium channels. These mediators increase the magnitude of the current, lead to activation of the channel at more hyperpolarized potentials, and enhance the rates of channel activation and inactivation. As a consequence, hypersensitivity can sensitize nociceptive neurons. In an experimental model of inflammatory pain in which an irritant was injected into the hind paw in rats, $Na_v1.7$ protein expression was upregulated within DRG neurons that project their axons to the inflamed area and such change increased excitability of these cells.[15] Collectively, these data suggest that $Na_v1.7$ contributes, at least in part, to pain associated with inflammation. Whether or not the stress (without inflammation) is one of the causes resulting in a dynamic change of $Na_v1.7$ expression is unknown.

"$Na_v1.7$: stress-induced changes in immunoreactivity within magnocellular neurosecretory neurons of the supraoptic nucleus," reported by Black et al,[16] reveals a relationship between salty feeding and high level expression of $Na_v1.7$ in supraoptic nucleus in rodent, which potentially provided a biological animal model to understand the relationship of stress and change of voltage gated sodium channel in irritable bowel syndrome (IBS).

In the study, the rats were housed under a 12 hours-12 hours dark-light cycle, and fed with 2% NaCl (ad libitum) in their drinking water and unlimited access to food. The measurement of plasma osmotic pressure after such feeding was confirmed by hyperosmolarity (mOsm), i.e., 323.3 ± 4.8 in control rats, 353.2

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± 3.3 in salt-loaded rats ($P < 0.05$). The changes of $Na_v1.7$ expression were analyzed using immunocytochemistry by comparing $Na_v1.7$ immunofluorescence between two groups (6 control and 6 salt-loaded rats) after 7 days of salt loading. The authors found that salt-loading induced a substantial increase in the level of $Na_v1.7$ immunoreactivity in magnocellular neurosecretory cells of the supraoptic nucleus compared to magnocellular neurosecretory cells in control rats. In addition to the detection of greater numbers of magnocellular neurosecretory cells that displayed $Na_v1.7$ immunolabeling, the intensity of $Na_v1.7$ in some magnocellular neurosecretory neurons was markedly greater than that observed in magnocellular neurosecretory cells from control rats. Quantification of the mean intensity of $Na_v1.7$ signal within the circumscribed supraoptic nucleus demonstrated a significant up-regulation of $Na_v1.7$ in response to salt-loading challenge. These observations demonstrate that the level of $Na_v1.7$ protein in these cells is significantly increased in osmotically-challenged rats.

Comment

$Na_v1.7$ protein is dynamic, and is up-regulated in response to increased osmotic stress via salt-loading. Now that sodium channel isoform (including $Na_v1.7$) of magnocellular neurosecretory neurons can be manifested by osmotic stress imposed by salt-loading and through the systematic circulation, it is a logical hypothesis that the osmosis stress imposed by salty diet has possibly more severer influence on $Na_v1.7$ expression in sensory neurons of intestine and DRG that may contribute to IBS or functional bowel disorders. Upregulation of $Na_v1.7$ may result in visceral hypersensitivity which may present with symptom as hyperalgesia; while elevation of prostaglandin, adenosine and serotonin, which have been reported in IBS, may shift the activation of $Na_v1.7$ left, i.e., resulting in symptom as allodynia. Obviously, the role of $Na_v1.7$ in IBS is worth to be explored.

Up to date, there is no direct evidence to link salty food with the dynamic change of expression in voltage gated sodium channel in enteric sensory neuron or visceral associated DRG neurons; also, there is no direct evidence to indicate $Na_v1.7$ as a threshold channel to IBS. However, the observation of the dynamic change of channel expression is being accumulated. Firstly, in clinic, there is enough evidence indicating that eating, diet and nutrition are associated with IBS, certain foods and drinks are responsible for triggering IBS symptoms; large meals can cause cramping and diarrhea, so eating smaller meals more often, or eating smaller portions, may help IBS symptoms. Secondly, Clinical studies show that chronic stress plays an important role in the pathophysiology of IBS.[17] Altered visceral sensitivity with increased responses to colorectal distension consistently presents and is recognized as a hallmark of IBS in clinic.[18-20] Thirdly, in basic research, a study of the mechanism of stress-induced visceral hypersensitivity revealed that inhibition of cystathionine β-synthetase lowered the expression of endogenous hydrogen sulfide, a potent modulator of transient receptor potential vanilloid type 1 (TRPV1) and voltage gated sodium channel, significantly suppressed voltage-gated sodium channel currents of colon specific DRG neurons and reversed the enhanced expression of $Na_v1.7$ and $Na_v1.8$ subtypes.[21] These findings emphasize a crucial role of $Na_v1.7$ protein which is dynamic and up-regulated in response to increased stresses.

Similarly, the other cellular molecules such as KCNA4[22] and TRPV1[23] and cellular endogenous factors such as neural growth factor[23] and transforming growth factor[24] have been reported in relation to visceral hypersensitivity. Obviously, the present findings in which the molecules of $Na_v1.7$, $Na_v1.8$, KCNA4 and TRPV1 have been suggested to be associated with visceral hypersensitivity need for the further assessment under high salt feeding, based on the idea reported from Black et al.[16]

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