Voltage-gated Na\(^+\) channels (VGSCs) are responsible for the rising phase of the action potential in excitable cells, including neurons and skeletal and cardiac myocytes. Small alterations in gating properties can lead to severe changes in cellular excitability, as evidenced by the plethora of heritable conditions attributed to mutations in VGSCs highlighting the need to better understand VGSC regulation. In this issue of the *JCI*, Hund et al. identify the ability of a key structural protein, β\(_{IV}\)-spectrin, to bind and recruit Ca\(^{2+}\)/calmodulin kinase II to the channel at a cellular location key to successful action potential initiation and propagation, where it can mediate function and excitability.
In excitatory tissues, such as muscle, heart, and nerve, action potential (AP) initiation is most often accomplished by the opening of voltage-gated Na$^+$ channels (VGSCs). VGSC activity is critical for normal impulse conduction and contributes to control of the duration and morphology of the cellular action potential, as well as the control of the duration and morphology of the nerve action potential. 

**The Na$^+$ channel and disease**

The sodium channel is a transmembrane protein that is responsible for the generation of the action potential. The channel is composed of four subunits: two alpha subunits and two beta subunits. The alpha subunits are responsible for the voltage-dependent gating of the channel, while the beta subunits are responsible for the regulation of the channel. The sodium channel plays a critical role in the transmission of nerve impulses and the contraction of muscle cells.

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VGSCs also form macromolecular complexes with the α subunit, having been shown to interact with numerous proteins, including a β subunit, ankyrin, syntrophin, dystrophin, fibroblast growth factor homologous factor 1B, calmodulin, and Nedd4-like ubiquitin-protein ligases (Figure 2B), all of which are involved in the regulation of channel activity, correct cellular localization, and biosynthesis and degradation of the α subunit (11, 12). Mutations in a number of these interacting proteins have been associated with inherited disease, including variants 4, 10, and 12 of long QT syndrome (13, 14). Another protein shown to regulate VGSCs primarily in — but not limited to — cardiac muscle, including an effect on late Na+ current, is Ca2+/calmodulin kinase II (CaMKII; refs. 15, 16). In addition to having an effect on VGSC current, CaMKII has been shown to be upregulated in heart failure and may therefore be a therapeutic target (17, 18). In this issue of the JCI, Hund et al. use sequence analysis to identify βn-spectrin as a CaMKII binding protein that participates in the Na+1.5 macromolecular complex in cardiac myocyte intercalated discs (ref. 19 and Figure 2B). Therefore, βn-spectrin appears analogous to the more ubiquitous AKAPs in that it recruits a kinase to a local signaling environment involving an ion channel. Moreover, Hund et al. found that βn-spectrin was required for the action of CaMKII on Na+1.5 (19). In mouse cardiomyocytes, abolishing CaMKII activity via a mutation in βn-spectrin positively shifted baseline Na+ channel steady-state inactivation (SSI) and eliminated the late Na+ current and SSI shift normally induced by β-adrenergic receptor stimulation by isoproterenol. Hund and colleagues further demonstrated that this was caused by βn-spectrin directly regulating CaMKII-mediated phosphorylation of a specific serine residue in the Na+1.5 I–II linker, S571. Consistent with the present understanding of the functional role of Na+ channel activity in the heart, the hyperpolarizing shift in SSI observed in mice expressing mutant forms of βn-spectrin led to reduced excitability, and the decrease in late current resulted in shortened APD and a subsequent decrease in the modulation of ion currents, including late Na+ current, that is bound by several local anesthetic drug molecules (5–7). In addition to a role in heritable disease (including long QT and epilepsy), emerging evidence has revealed that aberrant late Na+ current may play a role in the advanced stages of heart failure (8). Therefore, understanding not only the structures within the VGSC α subunit, but also the molecular identity of partner proteins that modify Na+ channel function is critical to the understanding of a number of complex disease phenotypes.

The Na+ channel as a macromolecular complex

Our understanding of ion channels as macromolecular complexes that tightly control channel function and regulation has grown in recent years (9). For example, in a number of PKA-sensitive ion channel complexes, the primary pore-containing subunit is in complex with an A kinase–anchoring protein (AKAP) that recruits kinase, phosphatases, and phosphodiesterases to control the local phosphorylation state (10).

VGSCs activate and inactivate completely within the first few milliseconds of the AP, thus very quickly reducing or eliminating their contribution to AP waveform. When VGSCs fail to inactivate normally, the resulting late (i.e., not inactivated) Na+ current provides a substantial inward current that prolongs AP duration (APD) and can lead to arrhythmia, either directly through the altered AP waveform or indirectly via altered intracellular Na+ concentrations. In recent years, a great deal of effort has been put into understanding the role of this late Na+ current and the therapeutic benefits of its blockade (4). Late Na+ current is preferentially blocked by a large number of drugs that interact with the pore-forming region of the α subunit at a well-described site that is bound by several local anesthetic drug molecules (5–7). In addition to a role in heritable disease (including long QT and epilepsy), emerging evidence has revealed that aberrant late Na+ current may play a role in the advanced stages of heart failure (8). Therefore, understanding not only the structures within the VGSC α subunit, but also the molecular identity of partner proteins that modify Na+ channel function is critical to the understanding of a number of complex disease phenotypes.

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in QT interval. The finding of Hund et al. that $\beta_{IV}$-spectrin associated with CaMKII in cerebellar Purkinje neurons targeting it to the axonal initial segments — critical regions for the generation of APs in which VGSCs localize — suggests that the key modulatory roles of $\beta_{IV}$-spectrin may very well exist in the brain, and perhaps other tissues, in addition to the heart.

**Conclusions and perspective**

There has been increasing understanding that ion channels do not exist on cell membranes simply as pore-forming proteins, but are instead in complex with a host of proteins that can influence the channel in a multitude of ways, including aiding channel targeting to specific subcellular regions, controlling the phosphorylation state of the channel, participating in biosynthesis and degradation of the channel, and altering channel gating allosterically. The present study by Hund et al. increases our understanding of the molecular identity of the complex controlling the phosphorylation state of the predominant cardiac VGSC (19). As phosphorylation of the channel affects channel-gating properties (i.e., SSI and late Na$^+$ current), and small perturbations in these properties are linked to disease in a number of systems, understanding the molecular components in this pathway represents a significant contribution to the field. Subsequently, this molecular pathway may represent a novel therapeutic target or serve as a new locus for heritable channelopathies. Furthermore, the ability of $\beta_{IV}$-spectrin to recruit CaMKII to distinct subcellular compartments critical to cellular excitability in other cell types may indicate a broader role within the cell, as it can serve not only as a structural protein, but also in the regulation of posttranslational states of membrane proteins.

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Obesity is associated with infiltration of white adipose tissue (WAT) by macrophages, which contributes to the development of insulin resistance. In this issue of the JCI, Kosteli and colleagues demonstrate that weight loss is unexpectedly also associated with rapid, albeit transient, recruitment of macrophages to WAT and that this appears to be related to lipolysis.

Macrophages are derived from monocytes and comprise a heterogenous population of cells found in nearly all tissues (1). In addition to their pivotal role in host defense, inflammation, and tissue repair, studies over the last decade have focused on their role in chronic metabolic diseases, such as obesity and insulin resistance (2). The role of inflammation and insulin resistance. In contrast, the role of innate and adaptive immunity in weight loss, the ultimate translational goal of research on obesity, is less clear. In this issue of the JCI, Kosteli and colleagues report that acute weight loss results in recruitment of macrophages to WAT (5). However, in this case, the recruited macrophages do not promote inflammation but rather regulate lipolysis. Since stimuli that enhance adipocyte lipolysis increase macrophage recruitment to WAT, the authors suggest that release of FFAs is a general signal for macrophage recruitment.

Obesity, inflammation, and macrophages
The chronic, low-grade inflammation that is characteristic of obesity has long been suspected to contribute to the development of insulin resistance (6). Almost two decades ago, Spiegelman and colleagues demonstrated that TNF-α, which is induced in the adipose tissue of obese animals, inhibits glucose disposal by promoting insulin resistance in peripheral tissues (7). Although adipocytes were identified as the source of TNF-α, expression of TNF-α was also observed in the stromovascular fraction rich in immune cells. This observation fueled a new direction in metabolic research and led to the discovery that macrophage infiltration of WAT is responsible for obesity-associated inflammation (3, 4).

While WAT from lean animals contains a resident population of alternatively activated macrophages (also known as M2 macrophages), which are characterized by expression of F4/80, CD206, and arginase 1 (Arg1), obesity is associated with recruitment of classically activated macrophages (complex is essential for membrane excitability in mice. J Clin Invest. 2010;120(10):3508–3519.

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Commentaries

In obesity and weight loss, all roads lead to the mighty macrophage

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