0022-1767/85/1352-787S$02.00/0
THE JOURNAL OF IMMUNOLOGY

Vol. 135, No. 2, August 1985,
Printed in U.S.A.

ELECTROIMMUNOLOGY: THE PHYSIOLOGIC ROLE OF ION CHANNELS IN THE IMMUNE SYSTEM[1]

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The recent development of the gigaohm seal voltage clamp technique has provided an approach to study individual cells of the immune system. Six distinct types of ion channels, most resembling channels found in nerve and muscle, have been identified in immune cells. Some of these channels appear to play important roles in various aspects of immune function. This article summarizes recent studies on ion channels in lymphocytes and macrophages.

The immune and neuroendocrine systems receive and respond to an almost unlimited array of diverse stimuli and retain a memory of the interaction. A complicated network of cell-cell interactions is utilized to achieve this degree of versatility. It is well known that ion channels are essential to the function of excitable cells, nerve and muscle. This paper summarizes recent studies which describe several types of ion channels present in the membranes of cells of the immune system. While their precise physiologic function has not yet been completely worked out, there is growing evidence that ion channels play an essential role in various aspects of cell function. In this brief review, we focus primarily upon T lymphocytes and the role of a potassium ion-selective channel in activation by mitogens. Ion channels present in B lymphocytes, natural killer cells, and macrophages are also discussed.

Ion channels. Ions traverse cell membranes in a variety of ways, their distribution across the membrane being responsible for the membrane potential. Ions may be transported passively down their electrochemical gradient through ion channels or by ion carriers or exchange mechanisms. Ions may also be actively transported "uphill" by energy-dependent pumps such as Na-K ATPase. In this paper we deal exclusively with ion channels, which are capable of transporting large numbers of specific ions across cell membranes, a process which can be controlled by the cell on a very brief time scale. Ions channels are pores formed by integral membrane proteins. These pores may be open (conducting) or closed (nonconducting). Transitions between open and closed states are termed "gating." Gating can be regulated in different ways. The probability that a "voltage-gated" channel will open depends in a predictable manner directly upon the cell membrane potential. Binding of extracellular ligand to specific cell receptors may directly open "ligand-gated" channels such as the acetylcholine receptor channel, or it may modulate channel function indirectly via an intracellular second messenger, as in the case of cardiac β-receptor-modulated Ca^{2+} channels. Many channels are modulated by more than one of these mechanisms, as in the case of Ca^{2+}-activated K^+ channels, whose voltage dependence is a function of the cytoplasmic free Ca^{2+} concentration. Several dozen distinct types of ion channels are known, characterized by their selective permeability to specific ions, by their voltage dependence, conductance, and gating kinetics, and by their sensitivity to specific drugs and toxins (reviewed in Reference 1).

Ion channels have been studied extensively in excitable tissues. In part, this has been so because they clearly play an important role in these cells, but, in part, the choice of preparation has been dictated by experimental necessity. The squid giant axon, with a diameter of 500 μm or more allows wire electrodes, along with capillary tubes for internal perfusion, to be inserted longitudinally for voltage clamp recording. Conventional electrophysiologic techniques, in particular the intracellular microelectrode, are useful only in moderately large cells. Insertion of a conventional microelectrode into any cell results in an unavoidable electrical leak around the electrode. In a large cell with thousands or millions of ion channels in its membrane, this leak current may be insignificant, but in a small cell such as a lymphocyte, the electrode leak current may be much larger than that flowing through ion channels in the membrane. The gigaohm seal recording technique (reviewed in Reference 2) has revolutionized research on small cells, making it possible to record faithfully currents as small as those flowing through single ion channels, a few pA (picoamperes = 10^{-12} amperes) or less. This capability presents the unique opportunity to study the behavior of a single protein moiety, an individual ion channel, in a small cell. In the "patch-clamp" technique a fire polished glass micropipette with a tip diameter of about 1 μm is filled with a solution of known ion composition. An electrode, usually a chlorided silver wire housed inside the pipette, measures the current between the pipette and a bath electrode. The pipette is pressed against the surface of a cell and then gentle suction is applied, which, under favorable conditions, results in formation of a tight electrical seal (with a resistance of several gigaohms; (giga = 10^9) between the pipette and the membrane. This "cell-attached patch" conformation enables measurement of discrete steps of current corresponding to opening and closing of single ion channels in the patch. A large pulse of suction applied to the pipette interior can be used to rupture the membrane patch at the tip of the pipette, resulting in conti-

[1] This work was supported by National Institutes of Health Grants NS14609, AI-20717, and AG-04361 and a fellowship to K.G.C. from the Southern California Affiliate, American Diabetic Association.
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nuity of the cytoplasm and the pipette solution—the "whole cell conformation." The physical stability of the pipette glass-to-membrane seal minimizes the leakage current under the pipette. The pipette solution rapidly equilibrates with the cytoplasm permitting control of intracellular ion concentrations. Electrically, the cell is voltage-clamped to the potential within the pipette, and thus the membrane potential can be experimentally controlled while ion currents passing through the entire cell membrane are recorded. Ion channels in the cell membrane can thereby be identified and characterized on the basis of their voltage dependence, kinetics, and pharmacologic properties.

Ion channels control a variety of cellular processes. They are responsible for action potentials, transmitter release, and postsynaptic responses, and are thus absolutely essential for muscle contraction, the heart beat and all neural activity. They also play a role in the secretion of hormones. Abnormalities of ion channels contribute to the pathogenesis of myotonia congenita and myasthenia gravis. Major functions of immune cells include chemotaxis, cell growth and proliferation, production and secretion of antibodies and lymphokines, and killing of foreign or virus-infected cells. We and several other workers have studied the involvement of ion channels in several of these processes. Thus far, five types of channels resembling ion channels found in excitable cells have been reported in various cells of the immune system: a voltage-gated K^+ channel with properties similar to those of the delayed rectifier in nerve or muscle (3–7), a voltage-gated Na^+ channel (5) that seems indistinguishable from that found in nerve or muscle, a voltage-gated Ca^{2+} channel with many similarities to Ca^{2+} channels in nerves (8, 9), a Ca^{2+}-activated K^+ channel (10), and an inwardly rectifying K^+ channel (7) that turns on when the membrane is hyperpolarized. Another type of channel is formed by macrophage Fc receptors in bilayers (11). Here we summarize recent studies in which electrophysiologic techniques have been combined with standard immunologic and biochemical methods in order to elucidate the role of ion channels in various aspects of immune function.

T lymphocyte activation. Several lines of evidence suggest that two signals are required for T cell activation: one Ca^{2+} dependent and the other macrophage or phorbol ester dependent (12). These two signals initiate a series of events that culminate in cell division. Several workers have postulated the existence of Ca^{2+} channels and Ca^{2+}-activated K^+channels to account for the Ca^{2+} influx and the accompanying membrane hyperpolarization and increased K^+ fluxes, stimulated by mitogen (13, 14). This two-channel view of activation was supported by pharmacologic studies using Ca^{2+} channel blockers to inhibit mitogenesis (15), and quinine, a blocker (albeit nonspecific) of calcium-activated K^+ channels in other tissues, to inhibit mitogen-induced membrane hyperpolarization and K^+ fluxes (13). However, Ca^{2+} channels and Ca^{2+}-activated K^+ channels have not been observed in resting or mitogen-activated voltage-clamped human T cells (3–5). Although it is difficult to rule out the possibility that Ca^{2+} channels might be present under certain conditions, voltage-gated K^+ channels are present in virtually all T cells. Consequently, our studies have led to a different hypothesis to account for the membrane hyperpolarization, increased K^+ fluxes, and elevated cystosolic-free Ca^{2+} that accompany T cell activation, based upon a single type of channel—a voltage-gated K^+ channel.

About 300 to 500 voltage-gated K^+ channels are expressed in the average human T cell. The kinetic and pharmacologic properties of T cell K^+channels are very similar to those of "delayed rectifier" K^+channels in nerve and muscle cells (3, 5). The voltage dependence of these channels and maximum K^+ conductance are indistinguishable with free Ca^{2+} levels in pipette solutions ranging from 2 nM to 1 μM. Since the pipette solution equilibrates rapidly with the cytoplasm, this K^+ channel appears insensitive to free Ca^+ concentrations well beyond the physiologic range (3, 5).

The T cell mitogens phytohemagglutinin (PHA) and concanavalin A (Con A) cause K^+ channels to open more rapidly and at more negative voltages in voltage-clamped T cells (3, 5, unpublished data). In an intact T cell mitogens would increase the probability of K^+ channel opening at the resting potential, resulting in membrane hyperpolarization and increased K^+ fluxes. Based upon a kinetic model of K^+ channel gating, we estimate that at the normal T cell resting membrane potential of −50 to −70 mV (see Reference 5), 0.1 to 2 K^+ channels would be open at a given time. The estimated K^+ efflux through these open channels would be 10 to 400 attomoles (atto = 10^{-18}) per min per cell, a range encompassing measured passive K^+ efflux values in resting human lymphocytes (see Reference 5). Mitogens would approximately double the number of open channels, accounting for the rapid twofold increase in K^+ flux that has been reported (see Reference 5). One day after mitogen activation, the K^+ conductance in human T lymphocytes approximately doubles (4). Because activated T cells are larger than resting T cells, this result suggests that the density of channels in the membrane may be maintained after activation.

K^+ channel expression is strikingly different in human and mouse T cells. While quiescent human T cells express several hundred K^+ channels (3, 5), resting mouse T cells express a much smaller number of K^+ channels (16, unpublished data). Preliminary studies indicate that mitogen activation of mouse T cells after 1 day results in a substantial increase (roughly 10-fold) in the numbers of conducting K^+ channels per cell (16). In human T cells, increases in K^+ fluxes occur almost immediately after mitogen addition, while in mouse T cells, elevated in K^+ fluxes develop after a delay of 6 to 8 hr (17). The delay in mitogen-enhanced K^+ fluxes in mouse T cells may be related to the delay in the expression of additional conducting K^+ channels.

Voltage-gated K^+ channels in squid giant axons have been directly shown to be permeable to Ca^{2+} in experiments using high Ca^{2+} concentrations, passing about 1% as much Ca^{++} current as K^+ current (18). This lack of perfect ion-selectivity is not unusual. Na^+ channels also exhibit a small degree of Ca^{2+} permeability, and monovalent cations can pass through Ca^{2+} channels (1, 19). Based upon the Ca^{2+} permeability of K^+ channels in squid, we estimate that about 4000 Ca^{2+} ions per sec might enter the T cell through each open K^+ channel (5). Although this level of permeability to Ca^{2+} seems very low compared with that for K^+, the calculated current carried by Ca^{2+} through K^+ channels is only about an order of

magnitude lower than the current carried by Ca^{2+} through Ca^{2+} channels at physiologic levels of Ca^{2+} (19), partly because the conductance of K^+ or Na^+ channels is much larger than that of Ca^{2+} channels. If mitogen or antigen opened one additional K^+ channel, the intracellular-free Ca^{2+} concentration in the absence of buffering would double in about 3 sec; due to cytoplasmic buffering the free Ca^{++} levels would rise more slowly. According to this hypothesis, Ca^{2+} entry into the T cell through K^+ channels would not depolarize the cell membrane because the net K^+ channel current would be outward; this is consistent with the observation that mitogens hyperpolarize the membrane (13).

In collaboration with Dr. Roger Tsien (University of California, Berkeley) we used the Ca^{2+} indicator dye, quin-2, to test whether K^+ channels in human T cells allow Ca^{2+} entry after mitogen stimulation. The intracellular-free Ca^{2+} concentration in resting T cells was about 120 nM and rose to about 230 nM after PHA addition. This rise in Ca^{2+} was partially inhibited by pretreatment with concentrations of 4-aminopyridine (4AP) or verapamil sufficient to block most K^+ channels. Addition of the blockers after the PHA-induced rise in cytoplasmic-free Ca^{2+} reduced free Ca^{2+} partway toward resting levels. These results are consistent with the idea that at least part of the Ca^{2+} entry into human T cells occurs through open K^+ channels. Electrically silent Ca^{2+} entry pathways such as passive carriers or ion exchange mechanisms are also a possibility. Thus, our studies on human T cells show that mitogens have a modulatory effect on K^+ channel gating that can account for membrane hyperpolarization, K^+ fluxes and at least part of the increase in cytosolic-free Ca^{2+} during T cell mitogenesis.

We have used a pharmacologic approach to determine whether the K^+ channel is necessary for mitogen-induced proliferation. A number of chemically unrelated substances, including "classical" blockers of K^+ channels in nerve and muscle (tetraethylammonium (TEA) and 4AP), Ca-activated K^+ channel blockers (quinine and cetiedil), a variety of calcium channel antagonists (verapamil, diltiazem, nifedipine, nitrendipine, and several polyvalent cations), calmodulin inhibitors (trifluoperazine and chlorpromazine), and a β-receptor blocker with local anesthetic properties (propranolol), all blocked K^+ channels in human T cells, many at micromolar concentrations (3, 20, 21, unpublished data). At similar concentrations, those blockers that have been tested, namely, 4AP, TEA, quinine, verapamil, nifedipine, cetiedil and diltiazem, reversibly inhibited ^{3}H-thymidine incorporation (3, 20, 22, unpublished data). In addition, propranolol and chlorpromazine inhibit PHA-induced ^{3}H-thymidine incorporation in murine T cells (23). Inhibition of mitogenesis was not due to nonspecific toxicity (3, 20, 22, 23). Mitogen-stimulated total protein synthesis was inhibited in a dose-dependent manner by the K^+ channel blockers 4AP, TEA, and quinine; interleukin 2 production and secretion were also inhibited by 4AP. Block of mitogenesis by 4AP was effective only if added during the first 20 to 30 hr of stimulation with mitogen (20). Surprisingly, expression of the interleukin 2 receptor is not inhibited by K^+ channel blockers (4AP, TEA, quinine) at concentrations that inhibit protein synthesis (20). This result suggests that the signals leading to the expression of the interleukin 2 receptor may not be mediated via the K^+ channel. In contrast, however, Birx et al. (22) report that verapamil inhibits Con A-induced expression of the interleukin 2 receptor on human lymphocytes. Allogeneic mixed lymphocyte stimulation is also inhibited by K^+ channel blockers (4AP, TEA, quinine) (20), as is the stimulation of the D10 T cell line, either by Con A or by a clonospecific antibody to the T cell antigen receptor (inhibited by 4AP, TEA, quinine, verapamil and diltiazem, unpublished studies in collaboration with Dr. C. A. Janeway, Yale University). Collectively, these data suggest that the K^+ channel in T cells is required for early events leading up to protein synthesis which take place during the first day during T cell activation. We are currently investigating whether other early events are K^+ channel-dependent.

A small fraction of human T cells express voltage-gated Na^+ channels closely resembling sodium channels in nerve and muscle. Sodium channels appear not to be involved in T cell activation, because the specific Na^+ channel blocker tetrodotoxin (TTX) had no effect on mitogenesis (5).

In summary, K^+ channels appear to play a vital role in T lymphocyte activation. K^+ channels may function as signal transducers, linking receptors on the outside of the cell with intracellular events during T cell activation, or they may be required for other early stages of the activation process.

Cell killing. Voltage-gated K^+ channels are present in clonal murine and in human cytotoxic T lymphocytes (24, unpublished data). Both Na^+ and K^+ channels are present in two murine natural killer (NK) cell lines (unpublished studies in collaboration with Dr. Gunther Dennert, University of Southern California). Several lines of evidence suggest that K^+ channels are required for target cell lysis. Conjugation of cytotoxic T cells with target cells during the lethal hit phase is accompanied by increases in K^+ conductance and ^{86}Rb efflux (24). K^+ channel blockers reversibly inhibit target cell lysis by human cytotoxic T cells and by natural killer cells, in a dose-dependent manner, at roughly the same concentrations that block the K^+ channel in these cells; tetramethylammonium (TMA), an analog of TEA, neither blocks the K^+ channel nor inhibits T cell killing (unpublished data). The exact role of the K^+ channel in T cell and natural killer cell-mediated cytotoxicity remains to be determined. Although large sodium currents were present in clonal murine natural killer cells, the sodium channel blocker TTX had no effect on natural killer cell-mediated cytotoxicity (unpublished data).

B lymphocytes and plasma cells. Involvement of ion channels in B lymphocyte or plasma cell functions, including expression of activation antigens, capping, differentiation, and antibody production and secretion, is suggested by a large body of indirect evidence. A discussion of the correlations between ionic fluxes, membrane potential changes, increases in intracellular Ca^{2+}, and various types of activation parameters is beyond the scope of this review. Recent patch clamp studies reveal differences in the ion channel expression of B cells compared with T cells. Human peripheral B lymphocytes express K^+ channels similar to those in human T cells, but the number of channels per cell seems to be smaller and more variable (unpublished data).

A more dramatic difference between T and B derived cells is that voltage-gated Ca^{2+} channels have been de-

tected in the nonsecreting S194 myeloma cell line and in two immunoglobulin-secreting hybridoma B cell lines (8, 9). The density of Ca^{2+} current in these cells increased after addition of fresh culture medium in parallel with the secretion of immunoglobulin, but not with the degree of proliferation. The Ca^{2+} channel antagonist D600 suppressed both cell proliferation and immunoglobulin secretion, the latter to a greater extent. However, D600 was a rather weak Ca^{2+} current blocker in these cells; thus, the pharmacologic evidence does not strongly support a link between Ca^{++} channels and immunoglobulin secretion (9). Ca^{2+} channels in clonal hybridoma cells are insensitive to the calcium channel antagonists nifedipine and nitrendipine as well (Dr. S. Hagiwara, personal communication). Surprisingly then, voltage-gated K^+ channels in lymphocytes appear to be more sensitive to agents generally considered to be Ca^{2+} channel antagonists than are Ca^{2+} channels in lymphocytes.

Macrophages. Recent studies with the gigaohm seal technique have confirmed and extended earlier studies (reviewed in Reference 25) suggesting that macrophages express ion channels. Human macrophages cultured for several days display action potentials suggesting the existence of an inward current channel, presumably permeable either to Na^+ or Ca^{2+} ions (26). A voltage-gated K^+ channel closely resembling the one in human T cells is present under some conditions in peritoneal mouse macrophages. No ion channels were detected 1 to 5 hr after isolation, but nearly all cells expressed delayed rectifier K^+ channels after 1 day in culture (6). A Ca^{2+}-activated K^+ channel has been identified in human peripheral blood monocytes/macrophages cultured for varying periods up to 3 wk (10). Different ion channels are expressed in the mouse macrophage cell line J774.1 at various times after plating, during the process of adherence (7). At first, no ion channels were detected. Outward K^+ current through a delayed rectifier K^+ channel appeared 2 to 6 hr after plating. Inward rectifier K^+ channels became prominent at later times, while the delayed rectifier K^+ current diminished, reaching 0 at 24 hr. There is some evidence that ion channels may play a role in phagocytosis and cytokine secretion by macrophages. Quinine, which blocks the delayed rectifier K^+ channel in T cells, has been reported to inhibit phagocytosis by mouse peritoneal macrophages and the J774 macrophage cell line (27). This inhibitory effect may be mediated by blockade of macrophage-delayed rectifier K^+ channels, or of calcium-activated K^+ channels. Preliminary studies in our laboratory indicate that interleukin 1 synthesis by human peripheral blood monocyte/macrophages is inhibited by the K^+ channel blocker 4AP, in a dose-dependent manner.

Interaction of ligands (e.g., IgG-coated erythrocytes) with the mouse macrophage Fc receptor transiently increases cytosolic-free Ca^{2+}, triggers phagocytosis and the secretion of various mediators of inflammation, and increases Na^+/K^+ fluxes across the membrane (see References 11 and 27). The elevation in intracellular free Ca^{2+} is only partially (70%) inhibited by the absence of extracellular Ca^{2+}, suggesting release of Ca^{2+} from intracellular stores, in addition to an influx from the outside (27). Purified mouse macrophage Fc receptor has been incorporated into planar lipid bilayers and shown to form a ligand-dependent monovalent cation-selective ion channel, sparingly permeable to Ca^{2+} (11). However, the great concentration difference in Ca^{2+} across the membrane may be sufficient to drive Ca^{2+} through the Fc-receptor channel, into the macrophage, providing a route for entry of extracellular Ca^{2+} (11, 27). In the absence of extracellular Ca^{2+}, macrophages are capable of phagocytosis of IgG-coated erythrocytes, at 40% of control levels (27). Buffering of intracellular-free Ca^{2+} by quin-2/AM, suppresses macrophage phagocytosis almost completely (27). Thus, intracellular-free Ca^{2+} levels seem to be more important for phagocytosis than the extracellular Ca^{2+} concentrations. The role of Ca^{2+} and the Fc receptor channel in interleukin 1 synthesis and antigen processing remains to be determined.

Implications. In conclusion, the patch clamp technique in combination with biochemical and immunologic methods has provided a new approach to study cells of the immune system. The studies discussed in this article suggest a crucial role for ion channels in initiating, regulating, and supporting many cellular functions, including proliferation. Future studies using this exciting new electroimmunologic approach may further clarify the link between ion channels and other intracellular signals such as protein kinase-C, diacylglycerol and cyclic nucleotides, and the role played by ion channels in various cellular functions and in cell-cell communication.

Acknowledgments. We gratefully acknowledge the technical help of Ms. Mary Thornton and Mr. Kevin Lee.

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