The effects of external and internal proton concentration on different cardiac $K^+$ currents are reviewed. Emphasis is given to the diversity of the changes: agonist, antagonist or both, effects from outside or inside. Possible underlying mechanisms, such as changes in gating or conductance and voltage-dependency are discussed.

I. Agonist effects

Acidosis, which is an important component of ischemia, enhances the open probability of the $I_{KATP}$, the $K^+$ channel inhibited by intracellular ATP(4, 6, 14). The underlying mechanism is double. The first is a shift of the inhibition-ATP concentration curve in such a way that higher concentrations are required to inhibit channel activity. This effect however is rather small in cardiac cells, when compared to the marked effect in skeletal muscle cells: in heart cells the $IC_{0.5}$ is only doubled while a 15-fold increase in concentration is observed in skeletal cells(5). The shift suggests a competition between protons and ATP, but since these molecules have opposite charges, the effect cannot be a direct one and a change in phosphorylation has been suggested. More recently another interesting mechanism for the increase in activity has been described in Kir6.2, a cloned inward rectifying $K^+$ channel that is activated in the absence of ATP(2). In this channel an histidine group in the C-terminal of the protein acts as a pore pH switch and modulates the block of the channel by spermine.
and spermidine. These molecules are partly responsible for the inward rectification in these channels. In acidosis the increased positive charge on the protein electrostatically repulses the polyamines, diminishes inward rectification and thus enhances outward current through the channel. The effect has also been confirmed in native cells.

A second K⁺ channel in which agonist effects have been described is the I⁰Kₐₐ, which is activated by arachidonic acid (AA) and negative pressure and thus may play a role in ischemia (13). Acidosis has been shown to enhance the sensitivity of this channel to pressure activation. At the molecular level, proteins of K⁺ channel family characterized by the presence of two pore domains and four transmembrane segments (e.g. TWIK) are good candidates (7).

II. Agonist and Antagonist effects
Agonist (9, 16) as well as antagonist (16) effects can be observed in I⁰, the transient outward current responsible for the fast initial repolarization during phase 1 of the action potential. When the holding potential is at a depolarized level full activation of the current by a large depolarization results in an I⁰ which is markedly potentiated in acidosis. In contrast when the holding potential is negative and activation is incomplete (moderate depolarization), the current is reduced. These opposite effects are due to shifts of the inactivation and activation curves in the positive direction. Similar effects can be observed by the addition of Cd²⁺ to the external perfusion solution (16). Competitive binding of H⁺ and Cd²⁺ to negative charges at an external site of the protein, affecting the voltage sensor, provides an explanation for these effects.

III. Antagonistic effects.
In cardiac cells I⁰ is responsible for the negative resting potential. Experiments at the single channel level have nicely shown that intracellular, but not extracellular acidosis reduces the open probability of the channel (10). The K₀.₅ is pH 6.11 and the Hill coefficient 2.52. The effect is due to a prolongation of the long closed time and is voltage-independent. Similar results have been obtained in expressed IRK1 channels (15). At the same time the single channel conductance is slightly reduced. A possible explanation is binding to the channel protein and an allosteric change of the channel kinetic behaviour; the small reduction in single channel conductance could also be due to a direct block of the channel pore.

A marked reduction in I⁰, the rapidly activated delayed K⁺ current, is seen upon exposure of the external side of the membrane to an acidic shift of the pH. Observations have been made in native cells (18) and on expressed hERG channels (1, 3, 11, 12, 17). The decrease in outward current is seen during the depolarizing pulse as well as for the tail currents obtained upon repolarization. The fall in current in native cells (18) can be analysed as being due to the following changes. 1) Steady-state activation is shifted in the positive direction (10 mV at pH 6.5), while the maximal level of outward current also undergoes a marked diminution. 2) The decay of the tail currents is markedly accelerated; the effect is especially pronounced at hyperpolarized levels. 3) The fully-activated current-voltage relation, obtained by measuring tail currents at different potential levels following a large depolarization (full activation), is reduced. The effect is voltage-dependent; at hyperpolarized levels the block may be so pronounced that extrapolation suggests a shift in the reversal potential; an increase in Na⁺ permeability however has been excluded, since identical results were obtained in the absence of intra- and extracellular Na⁺.

As possible underlying mechanisms two, perhaps three types of interaction may be responsible for the observed effects. 1) Surface charge change can explain the shift in activation. However, it cannot explain different shifts for steady-state activation and time constants of deactivation tails, nor the inhibition of the fully-activated current, or the absence of change in inward rectification (inactivation). 2) Voltage-dependent open-channel block by external protons provides an explanation for the acceleration of the tail currents and the shift in activation. In this respect, results obtained on I⁰ in rabbit sinoatrial node and hERG channels using different concentrations of Ca²⁺, Mg²⁺, and protons should be mentioned. External bivalent ions were shown to block the current in a voltage-dependent way (8). The removal of this block with depolarization was responsible for the
voltage-dependent activation of the channel. These authors further showed that protons and bivalent ions competitively interacted with this block(12), suggesting that the pH-dependent shift of the activation curve is probably due to protons binding in a potential-dependent way to the same site as Ca$^{2+}$. 3) The decrease of the fully-activated current, which was also voltage-dependent, requires a supplementary mechanism, the nature of which is presently unknown.

**IV. Conclusions**

This short overview indicates that different cardiac K$^+$ channels are affected by protons in different ways: the current can be enhanced or inhibited and the effects can be elicited by an interaction at different sides of the membrane and by different mechanisms. These mechanisms include changes of gating and/or conductance. In ligand-activated channels the gating can be changed by a shift in the affinity for the ligand ($I_{KATP}$, $I_{KAA}$); in voltage-activated channels ($I_{To}$-$I_{Kf}$) or background channels ($I_{K1}$) by a surface charge effect or allosteric modulation. Direct interaction with binding sites in the pore may result in diminution of the single channel conductance ($I_{K1}$), or a decrease in inward rectification ($I_{KATP}$), or a voltage-dependent acceleration of the tail currents ($I_{Kf}$).

**References**