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R. Gasser, W. Klein

K\textsubscript{ATP}-channels are involved in a multitude of cardioprotective mechanisms: The shortening of the cardiac action potential with subsequent decrease of Ca\textsubscript{2+}-entry and reduction of contractile force (reduced O\textsubscript{2}-consumption), ischaemic K\textsubscript{ATP}-channel opening and preconditioning. Myocardial hibernation, another cardioprotective mechanism, is also initially triggered by the opening of K\textsubscript{ATP}-channels. Drugs, like K-channel-openers, hence, are beneficial in coronary heart disease. They support the physiological mechanisms of anti-ischaemic protection. This article describes the various phenomena of anti-ischaemic protection in great detail.

**Key words:** preconditioning, K\textsubscript{ATP}-channels, nicorandil

ATP-dependent potassium channels constitute a subpopulation of transmembrane potassium channels. Opening of the latter results from a decrease of cytoplasmatic ATP. There are, however, various other causes for the opening of these ion channels, for example changes in the relationship between cytoplasmatic ATP and ADP, changes of intracellular pH, adenosin as well as various nucleotides and, in particular, K\textsubscript{ATP}-channel openers such as diazoxide, nicorandil and others. The discovery of the K\textsubscript{ATP}-channel was made by Akinori Noma in 1983 [1]. Until 1990, however, the function of those channels in the heart had remained unknown. We were the first to describe their function in the context of myocardial ischaemia [2], and Daut and co-workers described simultaneously the function of those channels in the context of hypoxia in vascular smooth muscle [3].

In the meantime, a multitude of single channel analyses as well as molecular investigations were conducted. The exact molecular structure of those channels was revealed, and the channel was cloned [4]. Extensive investigations of our own group as well as other groups have shown that the opening of K\textsubscript{ATP}-channels constitutes a vital mechanism in the context of ischaemia protection [5–7]. Sulfonylureas are specific blockers of those channels and possibly interact thus with vital protective mechanisms of the heart. Hence, their use in type II diabetic patients with concomitant coronary heart disease is still a matter of discussion [4–7]. This could explain the high cardiovascular mortality, which had been seen in the seventies in UGPD-study in patients treated with sulfonylureas [8]. In contrast, in patients with coronary heart disease, K\textsubscript{ATP}-channel opening would constitute a supportive measure in the body’s battle against ischaemia. The following chapters shall explain the vital cardioprotective mechanisms, which are mediated by K\textsubscript{ATP}-channel opening.

**Electrophysiological investigations**

We used conventional as well as ion-selective microelectrodes in our experiments on isolated papillary muscle-strips and vascular smooth muscle, we also used voltage clamp and isolated perfused “Langendorff”-hearts, isolated superfused guinea-pig aorta, pig coronary arteries as well as bovine coronaries. Figure 1 shows our Laboratory of Experimental Cardiology in Graz. Figure 2 shows an isolated guinea-pig papillary-muscle which is immersed in a layer of paraffin-oil, simulating myocardial ischaemia. Reperfusion is then simulated by lifting the paraffin-oil layer electronically and reperfusing the preparation with normal Tyrode. Several microelectrodes measure ionic changes on the cell surface as well as in the cytoplasm. This model allows the exact simulation of the salient characteristics of ischaemia. These are: reduction of contractile force, rising of extracellular potassium, depolarisation of the cell membrane, shortening of the action potential, acidification of the cell surface and acidification of the intercellular...
larr spaces. It is noteworthy that myocardial ischaemia appears in three different forms: acute ischaemia, repetitive ischaemia and chronic ischaemia.

Acute ischaemia

In acute ischaemia, there are four salient mechanisms, which bring the heart from the ischaemic state back to the non-ischaemic state. These are:

1. The local reduction of contractile force in the ischaemic area and thus a reduction of oxygen consumption in this particular part of the myocardium
2. Reduction of pre- and afterload resulting from the liberation of the atrionatriuretic peptide (the strongest diuretic substance so far known in nature as well as a strong vasodilator which leads to the elimination of volume and simultaneously reduces peripheral resistance by vasodilation)
3. Pain, as seen as in angina which leads to an instantaneous cessation of physical activity by the patient
4. The hypoxic-ischaemic reactive coronary dilation which leads to an improvement of myocardial perfusion

1. Local reduction of contractile force in the myocardium

This phenomenon has been known for many years and occurs in the early phase of acute myocardial ischaemia. It leads to an acute reduction of contractile force within seconds after the occurrence of ischaemia. This local phenomenon protects the heart from oxygen and energy consumption. There are numerous cellular and molecular mechanisms which are involved in this phenomenon: predominantly, it is the shortening of the action potential with a shortening of the plateau phase. The latter leads to a reduction of the net calcium influx which per se reduces contractility. Other mechanisms, like cellular acidification and subsequent desensibilisation of the contractile apparatus towards calcium as well as the increase of cellular magnesium competing with calcium ions on the contractile apparatus and the fall of cytoplasmic high-energy phosphate also constitute mechanisms, but lead to local reduction of contractile force in the myocardium. However, the main part is played by the shortening of the action potential which has been described as early as in the forties. Our own investigations [2] (fig. 3) have shown that the shortening of the action potential is caused by an increase of transmembrane potassium conduction which is exclusively mediated by the opening of K\textsubscript{ATP}-channels. This increased transmembrane potassium conduction leads to a faster repolarisation. Figure 3 shows in panel B that a decrease in contractile force occurs early in acute ischaemia: the left part of panel B shows the shortening of the action potential and its relation to contractile force. The right part of the panel shows that in the presence of tolbutamide, a specific blocker of K\textsubscript{ATP}-channels, the action potential shortening does not occur. Likewise, the fall in contractile force is much less pronounced. Thus, a blockade of K\textsubscript{ATP}-channels would have an unfavourable effect on the local reduction of contractile force which, in turn, would lead to more oxygen consumption of the ischaemic myocardial tissue. While the latter would enhance the progress to necrosis, one could argue that the application of low dose potassium channel openers in this context would lead to a faster shortening of the action potential and improve ischaemia protection.

2. Decrease of pre- and afterload secondary to the liberation of ANP

Despite the fact that this particular article is devoted to K\textsubscript{ATP}-channel opening, it is noteworthy that acute ischaemia also leads – by a loss of contractile force of the left ventricle – to an increase of enddiastolic pressure and, via the pulmonary circulation, to a subsequent increase in the right atrium. This leads to a liberation of atrionatriuretic peptide. It also has been shown that atrionatriuretic peptide can be liberated from ischaemic myocardium itself. Figure 4 shows an increase of ANP after a short ischaemic phase which has been caused by tran-
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**Figure 5.** Pig coronary artery precontracted with potassium-rich Tyrode solution:

A: When 100 % oxygen is switched to 100 % nitrogen in the perfusate (simulation of ischaemia) and instantaneous dilation of the artery occurs.

B: Tolbutamide, a specific blocker of K<sub>ATP</sub>-channels leads to an inhibition of these mechanisms, hypoxic vasodilation is inhibited.

C: Serial experiments on the inhibition of hypoxic coronary dilation using glibenclamide and other specific blockers of K<sub>ATP</sub>-channels.

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**Figure 6.** Phenomenon of aut preconditioning. During the early phase of acute myocardial infarction, various parameters of ischaemia are subject to changes: ST-elevation, CK-MB, myoglobin as well as ANP rise and fall in an episodic manner. They reflect alternating phases of coronary artery occlusion and spontaneous reperfusion. PTCA, in contrast, only causes one peak in the ANP-concentration curve, as we see only one occlusion and one reperfusion (see figure 4).

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3. Pain

It has been known for a long time that acute myocardial ischaemia causes anginal pain. This type of pain is mediated by various factors, in particular, by the accumulation of extracellular potassium ions (fig. 3) which is one of the salient characteristics of ischaemia. The increase of extracellular potassium leads to a depolarisation of free nerve endings and these, in turn, lead to anginal pain which subsequently causes instantaneous cessation of physical activity. The latter is invariably related to a reduction of cardiac workload. As a result, oxygen and high-energy consumption of the myocardium decreases, which is pivotal for anti-ischaemic myocardial protection. Figure 3 shows that this extracellular rise of potassium in the early phase of myocardial ischaemia is mediated by K<sub>ATP</sub>-channels. The presence of tolbutamide, a specific blocker of K<sub>ATP</sub>-channels completely abolishes the extracellular potassium accumulation in the early phase of myocardial ischaemia.

4. Myocardial ischaemia and reflectory coronary artery dilation

The so called reflectory coronary artery dilation, which occurs as a result of hypoxia or ischaemia, has been known for many years. In this context, many hypotheses have been put forward concerning the mechanisms involved in this phenomenon. One of them is the adenosin-hypothesis. Reference 7 gives an overview on this hypothetical concept. Many factors have been claimed to play an important role in this context, such as lactic acid, adenosin, prostaglandines, EDRF, a rise of extracellular potassium, the local acidification as well as the rise of free CO². It was shown by Daut in 1989 that the main part in coronary artery dilation is played by the opening of KATP-channels.

**Figure 5A** shows an experiment on a pig coronary artery which is exposed to hypoxia (100 % oxygen replaced by 100 % nitrogen in the perfusate). One can see a quick dilation of the coronary artery during hypoxia. In the presence of a specific blocker of K<sub>ATP</sub>-channels, one can see (fig. 5) immediate inhibition of hypoxic coronary dilation. Figure 5C shows results from several experiments where hypoxic coronary artery dilation is inhibited by glibenclamide, a specific blocker of K<sub>ATP</sub>-channels [11]. Experiments have been conducted with and without endothelium and showed that, in this particular setting, the endothelium plays just a minor role.
In summary, one can say that in acute ischaemia three mechanisms play an important role in anti-ischaemic myocardial protection: anginal pain, reflexory coronary artery dilatation and local reduction of contractile force.

**Repetitive ischaemia**

1. **Preconditioning**
   Preconditioning is a myocardial protective mechanism that follows a short ischaemic episode of several minutes. This is equivalent to a short anginal attack. If that short period of ischaemia is followed by a prolonged ischaemic episode, the myocardium is protected against ischaemic damage: contractile force returns to normal much faster and necrosis develops later. Recent works have shown that preconditioning is also mediated by KATP-channels. However, various second messengers in the cytoplasm induce the synthesis of protective proteins, like the heat-shock-protein and others. Preconditioning can be prevented by blocking KATP-channels. In contrast, the pharmacological opening of KATP-channels induces myocardial preconditioning [6]. There are also investigations on human myocardium that confirm these observations. It could be shown that patients who have been treated by specific openers of KATP-channels, in particular, nicorandil, indeed show preconditioning in the myocardium [6]. Necrosis occurs later in such patients. Hence, nicorandil and other KATP-channel openers show a cardioprotective action in addition to the ones already mentioned.

2. **Autopreconditioning**
   Years of investigations in our laboratories have shown that the early phase of myocardial infarction is phasic in its nature and shows waves of autoreperfusion alternating with coronary thrombosis and spasm [12]. Figure 6 shows different phasic phenomenon as occurring in early myocardial infarction, representing waves of spontaneous reperfusion. Likely, the waves of reperfusion – similar to preinfarction syndrome and preinfarction angina – have been designed to precondition the myocardium in order to prevent severe ischaemic damage from the subsequent myocardial infarction. Thus, the phasic nature of early myocardial infarction with the waves of reperfusion very likely cause a phenomenon which could be called autopreconditioning.

**Chronic ischaemia**

**Hibernation**

Hibernation is a constitutive state of underperfused myocardium in which its contractile function is transiently reduced.

**a. Acute hibernation**

In order to understand the pathophysiology of hibernation, one has to distinguish between acute and chronic hibernation. The acute form of hibernation is induced by the opening of KATP-channels and the subsequent shortening of the action potential [13] (figure 3). The latter leads to a decreased net calcium influx which, as a second messenger, like other factors, leads to a molecular restructuring of the myocardium.

**b. Chronic hibernation**

Resulting from **a. acute hibernation**, molecularstructural changes occur in the myocardium likely as a result of decreased intercellular calcium (which acts as a second messenger), and itself results from a shortening of the action potential as described above. In principle, the myocardium becomes hypotrophic. This hypotrophy is based on a complex mechanism, which results from numerous molecular changes. It is important to reiterate that the ionic bases of chronic hibernation are constituted by the reduced net calcium influx.

In summary, hibernation constitutes a protective mechanism in which the myocardium is somehow switched off or reduced in its contractile function and thus protected from damage which could result from the reduced perfusion. Hibernation is confined to the underperfused myocardial regions and is reversible. Why does the heart hibernate? In real life, reduced coronary perfusion in a local area of the myocardium also leads to increased collateralisation and once the collateral vessels are sufficient to support the hibernating myocardium it reconstitutes its original contractile function. Hibernation plays an important part in the context of surgical revascularisation. Some authors even state that ischaemic cardiomyopathy with globally decreased left ventricular ejection fraction constitutes, a form of hibernation and therefore revascularisation of such patients is useful.

**Conclusion**

However, from the importance of KATP-channels in the context of ischaemia prevention one can deduce that KATP-channel opening is certainly beneficial for patients with coronary heart disease. The pharmacological inhibition of these channels, however, may be fatal for patients with coronary heart disease. Therefore, one should pay attention when using oral antidiabetic drugs on patients with coronary heart disease. Nicorandil, as well as all the KATP-channel openers, have proven beneficial in several clinical settings for patients with coronary heart disease. A large trial particularly designed on the investigation of nicorandil effect on mortality and morbidity is on the way.

**References**

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