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Evaluation of the cardiac safety of second-generation antihistamines

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Introduction

To date, the classification of antihistamines into older, or first-generation, drugs and the newer, or second-generation, drugs has been made on the basis of H_1 as opposed to muscarinic selectivity combined with a much-reduced tendency to cause sedation. Many second-generation antihistamines are available today, and, at first glance, there appears to be little to choose between them in terms of safety and efficacy. However, the second-generation drugs have very different chemical structures (1), with variations in therapeutic profile, side-effects, half-life, tissue distribution, metabolism, and degree of antiallergic efficacy. Thus, with the passage of time, it has become apparent that the newer antihistamines in fact represent a heterogeneous group of compounds. There has also been a great deal of concern regarding the possible cardiotoxic effects associated with some of the newer medications (2). This review will summarize recent progress in the study of the cardiac actions of second-generation antihistamines. We will also review some of our recent data which investigated the effects of astemizole, cetirizine, loratadine, and terfenadine on a specific class of potassium (K^+) channels (hERG) which is involved in the repolarization process of the cardiac action potential. This membrane protein regulating K^+ homeostasis has been studied by means of heterologous expression in *Xenopus* oocytes and mammalian cells; furthermore, in some experiments, we took advantage of the constitutive expression of hERG K^+ channels in human neuroblastoma cells such as the SH-SY5Y cells.

Cardiac tolerance of second-generation antihistamines

Although second-generation H_1-receptor blockers introduced the advantage of less sedation and anti-muscarinic action, thus improving their therapeutic value, some, but not all, of these new drugs have been recently discovered to cause other serious cardiovascular adverse reactions. Following the description of ventricular arrhythmia of the torsade de pointes type in patients taking astemizole (3, 4) or terfenadine (5, 6), the focus on the risk/benefit ratio of antihistamines, in addition to sedation, has shifted toward their propensity to induce cardiotoxic events. In fact, after careful review of several retrospective cases of association between terfenadine and cardiotoxic events, the US Food and Drug Administration has withdrawn terfenadine from the market in the USA. The European Commission has similarly decided to withdraw some terfenadine preparations (120-mg tablets and all terfenadine-pseudoephedrine tablet formulations) from the European market.

The cardiotoxic effects exerted by both astemizole and terfenadine have been often observed under conditions of overdose or when the drugs' metabolism, which occurs mainly via the liver cytochrome P450 CYP3A4, was reduced either by the concomitant administration of ketoconazole or macrolide antibiotics, or by pre-existing liver diseases (7). Additional factors predisposing to the development of cardiac arrhythmias by antihistamines include congenital QT prolongation, ischemic heart disease, congestive heart failure, and electrolyte imbalance such as hypokalemia

and/or hypomagnesemia (8). Thus, in conditions of overdosage or when compromised liver function results in reduced metabolism, the plasma concentration of terfenadine or astemizole can rise, leading to cardiac toxicity. On the other hand, from a clinical standpoint, it is important to emphasize that antihistamines are not the only drug class able to induce torsade de pointes ventricular arrhythmias, since other drugs belonging to various therapeutic classes, including antiarrhythmics, neuroleptics, antidepressants, vasodilators, corticosteroids, diuretics, prokinetics (cisapride), antibiotics, and poisons (arsenic and organophosphates), have also been shown to induce these adverse effects.

Mechanisms of cardiotoxicity

Several ionic currents – both inward and outward – contribute to cardiac myocyte repolarization; these currents are finely tuned throughout the action potential to give rise to its specific and characteristic shape in ventricular myocytes. The torsade de pointes caused by terfenadine and astemizole correspond to a progressive modification of the amplitude and polarity of the QRS complexes on the surface ECG, generally occurring under conditions of marked bradycardia with prolongation of the QT interval. Therefore, the prolongation of the cardiac action potential is a landmark for drugs able to cause torsade de pointes ventricular tachycardia.

The potential duration of ventricular action can be increased either by decreasing the potassium current or by increasing the inward current, either that of sodium or, particularly, calcium. Therefore, soon after the discovery of the cardiotoxic manifestation occurring with astemizole and terfenadine, a major effort was made to investigate the molecular mechanisms underlying such cardiotoxic effects by studying the effects of these drugs at the level of specific ion channels. Recent evidence has demonstrated that the described cardiotoxic manifestations associated with astemizole and terfenadine could be explained by their ability to interfere with a specific cardiac repolarizing current termed IKr (9, 10). The molecular basis of this cardiac repolarizing current has been clarified recently, as a result of the study of the molecular genetics of the long QT syndrome (LQTS), a congenital human cardiac arrhythmia. In fact, the electrocardiographic features of LQTS greatly resemble those of drug-induced torsade de pointes. Mutations in the gene encoding for IKr have been found in patients with LQTS (11). The K^+ currents encoded by this gene, denominated human ether-a-gogo-related gene (hERG), as it was cloned by sequence homology with the ether-a-go-go (EA) gene (12), were therefore soon considered to be a potential target in drug-induced arrhythmias.

The possible interaction of antihistamines with hERG K^+ channels can be studied either in cells where these channels are constitutively expressed, such as cardiac myocytes or human neuroblastoma cells (13, 14), or upon their heterologous expression in other cellular systems. An expression system often used by pharmacologists to study ion channels is the *Xenopus* oocyte, which can be microinjected with *in vitro* transcribed RNA derived from hERG cDNA. These cells can be used for electrophysiologic study of the heterologously expressed hERG K^+ channels by means of the two-microelectrode voltage clamp technique. About a year after the discovery of hERG K^+ channels as the main molecular determinants of the cardiac repolarizing current IKr, astemizole and terfenadine were found to block hERG K^+ channels with nanomolar affinity upon heterologous expression of these channels in *Xenopus* oocytes (15, 16).

These results raised the fundamental issue of whether the cardiac side-effect of second-generation antihistamines was a class property – i.e., whether all second-generation antihistamines shared the property of inhibiting hERG – and whether differences among them could be detected. The heterologous expression of hERG cDNA in *Xenopus* oocytes was recently used to compare the effects of terfenadine, astemizole, loratadine, and cetirizine on the inhibition of both inward and outward currents carried by these K^+ channels (14). Perfusion of an oocyte expressing hERG K^+ channels with 0.1, 1.0, or 10 μM astemizole results in a dose-dependent decrease in the current (Fig. 1). Similar results were obtained with terfenadine within the same concentration range. In contrast, superfusion of *Xenopus* oocytes with 1 μM loratadine had no effect, with a very slight inhibition observed at the 10-μM concentration (14). On the other hand, cetirizine at the same concentrations clearly did not show any interaction with this cardiac potassium channel. Perfusion with 30 μM loratadine gave a 20–25% inhibition of both the inward and outward components of the current, an effect which was reversed after washout of the drug, whereas application of the same concentration of cetirizine did not exert any inhibition in the same cell.

These data suggest that there are molecular determinants in these second-generation antihistamines which have clearly distinctive effects on this K^+ channel. Interestingly, the first-generation H_1-receptor blocker hydroxyzine, although structurally very similar, demonstrated inhibitory effects on the hERG potassium channel in *Xenopus* oocytes, which were significant at 3 and 30 μM (Fig. 2). Since hydroxyzine has an octanol/water distribution profile much higher than cetirizine in the physiologic pH range (17), it could be hypothesized that this higher lipophilicity of hydroxyzine allows better interaction with the drug-receptor site on the hERG K^+ channel. Moreover, high concentrations of cetirizine had no effect on a wide

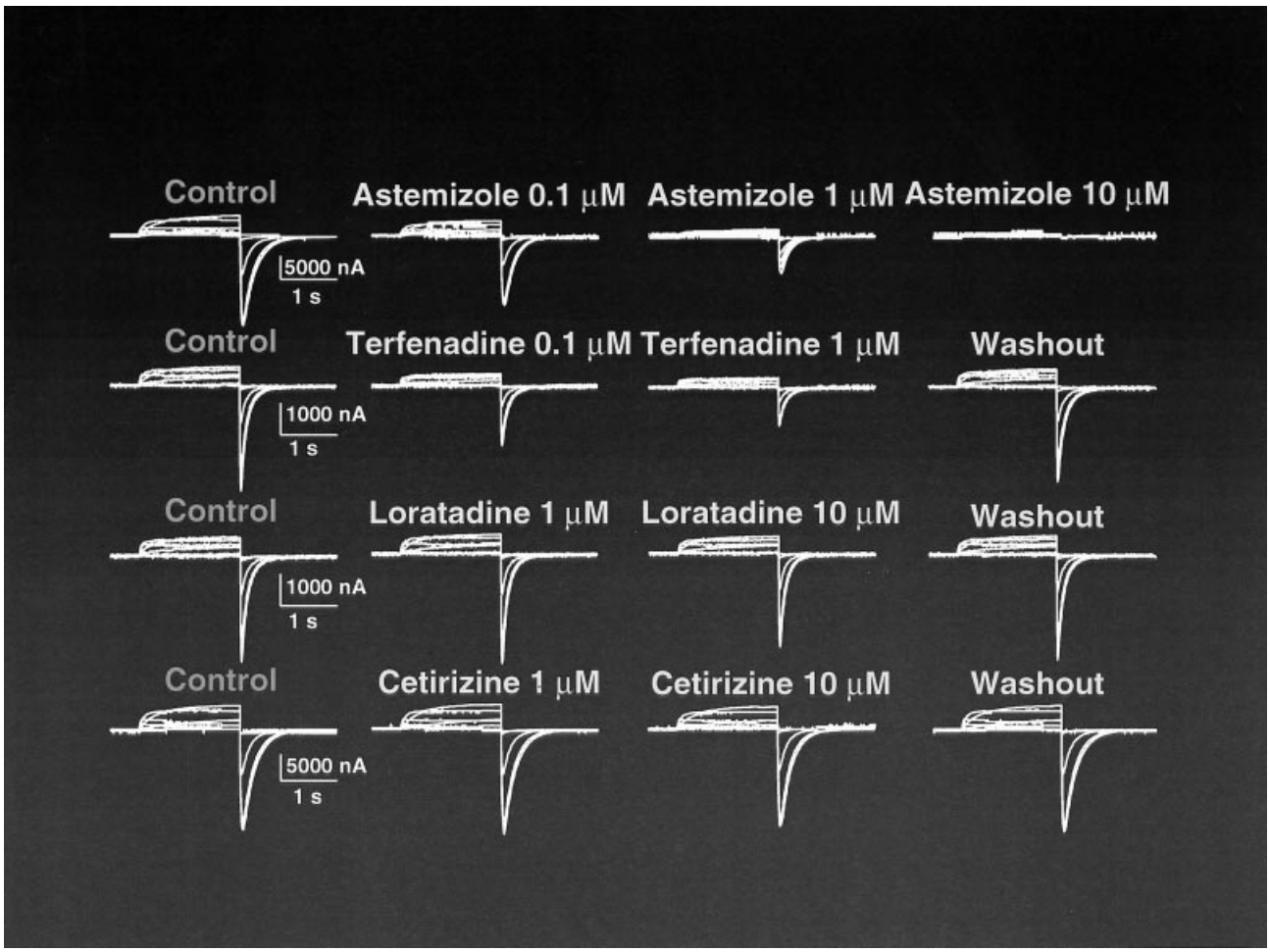

Figure 1. Effect of four different H_1-receptor antagonists, astemizole, terfenadine, loratadine, and cetirizine, on hERG K^+ currents expressed in *Xenopus* oocytes. Representative current traces recorded with two-microelectrode voltage-clamp technique from four different hERG-expressing oocytes recorded in control condition and after 5-min perfusion with indicated concentrations of each of four different H_1-receptor antagonists. Holding potential: −90 mV; test potentials from −80 to +40 mV in 20-mV steps; return potential: −100 mV.

range of K^+ channels expressed in *Xenopus* oocytes (Fig. 3). One problem with the use of *Xenopus* oocytes for these types of experiments is that drug penetration into the cell can be more difficult due to the presence of a layer of follicular cells surrounding the oocyte. The hypothesis that the lack of inhibitory action of cetirizine on IhERG in *Xenopus* oocytes is due to the relatively poor access of the drug to its putative intracellular receptor site on the channel was tested with the mammalian human embryonic kidney 293 (HEK 293) cells stably transfected with hERG cDNA (18). This expression system has the advantage of being amenable to patch-clamp recordings in the whole-cell configuration, a technique which allows access to the intracellular side of the membrane. Extracellular perfusion of hERG-expressing HEK 293 cells with astemizole (3 μM) completely blocked both the inward and the outward components of K^+ currents heterologously expressed in these cells, whereas cetirizine was completely ineffective (14).

To investigate whether cetirizine could be an effective blocker of IhERG when applied on the intracellular side of the membrane, we studied the time-course of the inward component of IhERG in hERG-transfected HEK 293 cells after gaining access to the cell interior in the presence and in the absence of the drug inside the recording pipette (Fig. 4A). In control conditions (no drug in the pipette), a 20% decrease of the inward K^+ current occurred after 20 min. When cetirizine (3 μM) was included in the patch pipette, the time-dependent reduction of IhERG in hERG-transfected HEK 293 cells was superimposable on that observed in controls (Fig. 4B). By contrast, if the same concentration of astemizole was added to the pipette solution, IhERG showed a marked time-related decline, being almost completely blocked after 20 min (95% blockade) (14). This suggested that an effective exchange between the pipette solution and the cell cytoplasm was occurring, because astemizole was able to diffuse from the pipette and thus reach its binding site, presumably located on

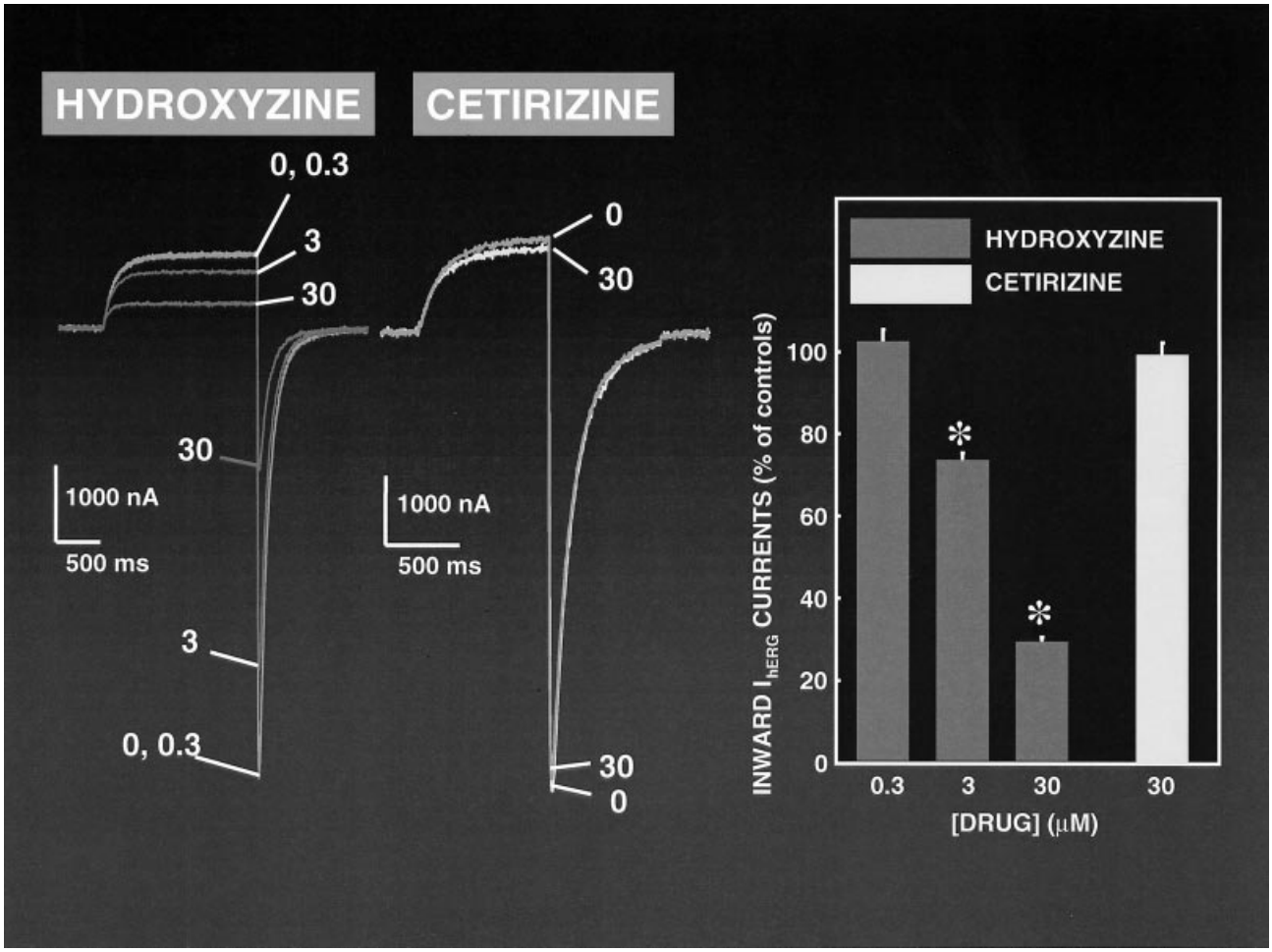

Figure 2. Differential effect of hydroxyzine and cetirizine on hERG K^+ currents expressed in *Xenopus* oocytes. Representative current traces recorded with two-microelectrode voltage-clamp technique from two hERG-expressing oocytes recorded in control condition, after 5-min perfusion with indicated concentrations (in μM) of hydroxyzine or cetirizine. Holding potential: −90 mV; test potential: 0 mV; return potential: −100 mV. Graph on right shows inhibition of IhERG by 3 and 30 μM hydroxyzine, as compared to lack of effect of comparable concentrations of cetirizine.

the cytoplasmic surface of the hERG K^+ channels. The observation that internally applied cetirizine failed to inhibit IhERG in hERG-transfected HEK 293 cells seems to suggest that the intracellular side of the channel molecule is insensitive to the drug, at least at the cytosolic concentrations reached in the present experiments. Therefore, it seems plausible to conclude that cetirizine lacks the ability to interact optimally with the terfenadine/astemizole receptor site on the intracellular side of the hERG K^+ channel molecule. To confirm the pharmacologic profile found in heterologous expression systems, we have also utilized a human neuronal cell line for our studies, SH-SY5H, which constitutively expresses the hERG potassium channels (13). Assessment of the effects of astemizole, terfenadine, cetirizine, and loratadine revealed effects on hERG potassium currents in the SH-SY5H neuroblastoma cell line like those seen in *Xenopus* oocytes. At a concentration of 3 μM, astemizole and terfenadine completely inhibited the inward rectifier K^+ current. Loratadine exerted some inhibitory effect when used in concentrations of 3 μM; in contrast, as before, cetirizine completely lacked inhibitory effect.

Interaction of antihistamines with the sympathetic nervous system

Since SHSY-5Y cells represent a useful model of the peripheral sympathetic nervous system, we have also studied the functional role played by hERG K^+ channels in the process of norepinephrine release from these cells. Therefore, the neuroblastoma cells were loaded with 3H-norepinephrine and allowed to release the neurotransmitter in response to increasing concentrations of extracellular potassium ions. This depolarization-induced 3H-norepinephrine release was found to be completely calcium-dependent; removal of calcium ions from the extracellular space, plus the addition of a calcium chelator, completely prevented this effect. Terfenadine and astemizole both caused a

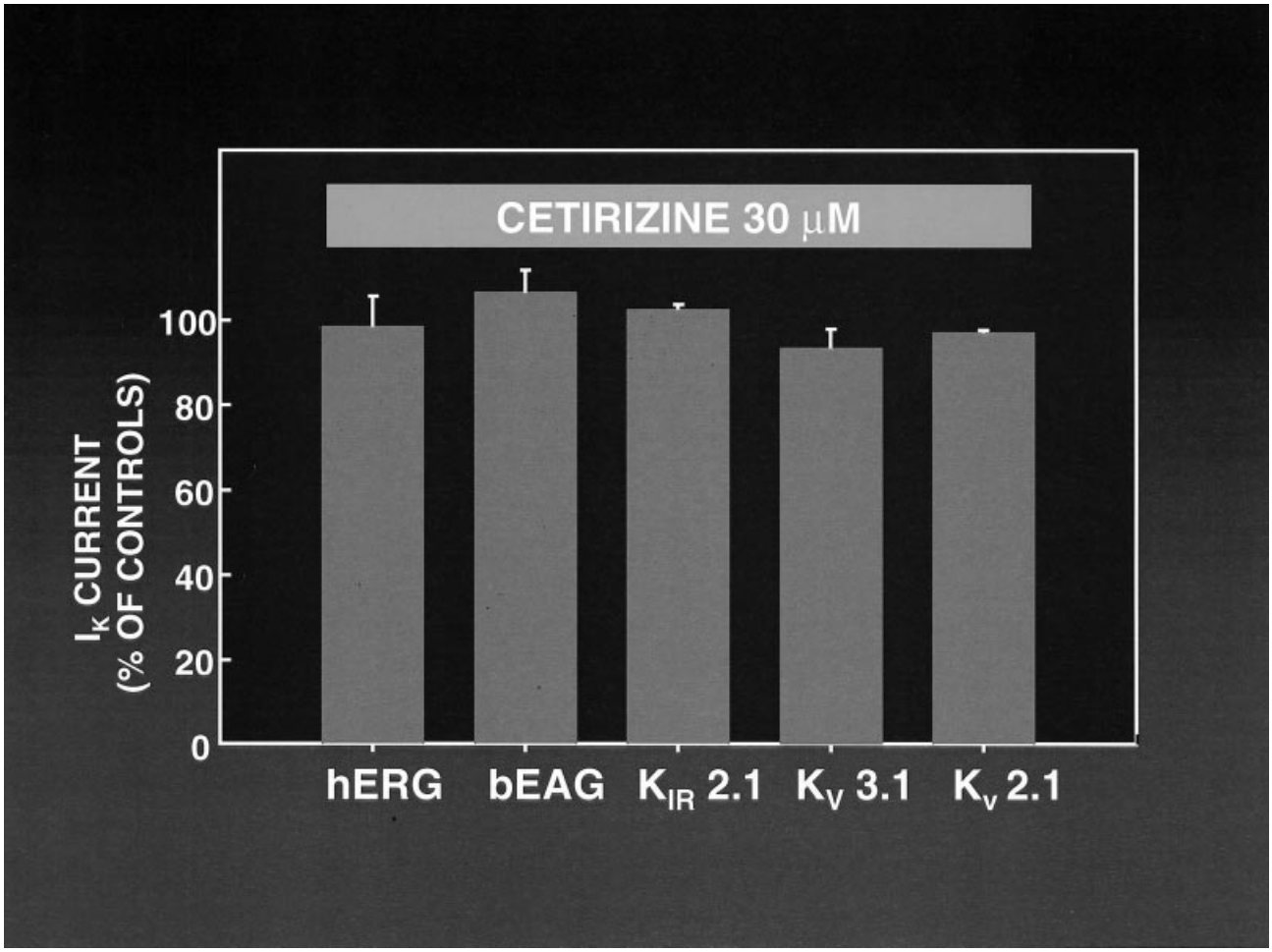

Figure 3. Lack of effect of cetirizine (30 μM) on different K^+ channels (hERG, bEAG, KIR 2.1, Kv 3.1, and Kv 2.1) heterologously expressed in *Xenopus* oocytes.

concentration-dependent (0.3–10 μM) inhibition of 3H-norepinephrine release elicited by high potassium concentration, while cetirizine, in concentrations up to 10 μM, had no effect in this system (Taglialatela et al., 1999, paper submitted for publication). On the one hand, these experiments might be useful to elucidate the role played by hERG potassium channels in neurotransmitter release in both the peripheral and central nervous systems, and, on the other hand, to clarify the potential role played by the sympathetic nervous system in the cardiotoxic effects exerted by some second-generation antihistamines and other drugs. The observation that hERG K^+ channels play an important role in sustaining the release of norepinephrine during high K-induced depolarization might be of considerable pathophysiologic relevance. In fact, polymorphic ventricular tachycardia of the torsade de pointes occurring with those H_1-receptor antagonists which block hERG K^+ channels can more easily occur if concomitant bradycardia exists. As a matter of fact, a first-line treatment for such serious cardiotoxic events is to increase the heart rate by isoproterenol administration (2, 19). Therefore, it may be possible that those H_1-receptor blockers with the potential for cardiotoxicity might not only exert their action potential-prolonging effect directly at the level of cardiac hERG K^+ channels, but also by blocking hERG K^+ channels in postganglionic sympathetic nerve terminals, so slowing heart rate by impairing the outflow of catecholamines. This latter phenomenon might contribute to the occurrence of the arrhythmic episode.

Studies on endocrine cells

In order to investigate the role played by hERG K^+ channels in the control of the resting membrane potential in the neuroendocrine cell line GH3, we have studied the effect of several second-generation antihistamines on the oscillatory pattern of intracellular calcium (Ca^{2+}) concentrations displayed by these cells. In these cells, the intracellular Ca^{2+} concentration displays continuous oscillations from 100 nM, which is the approximate baseline, to 400 nM. These intracellular Ca^{2+} transients are related to the release of

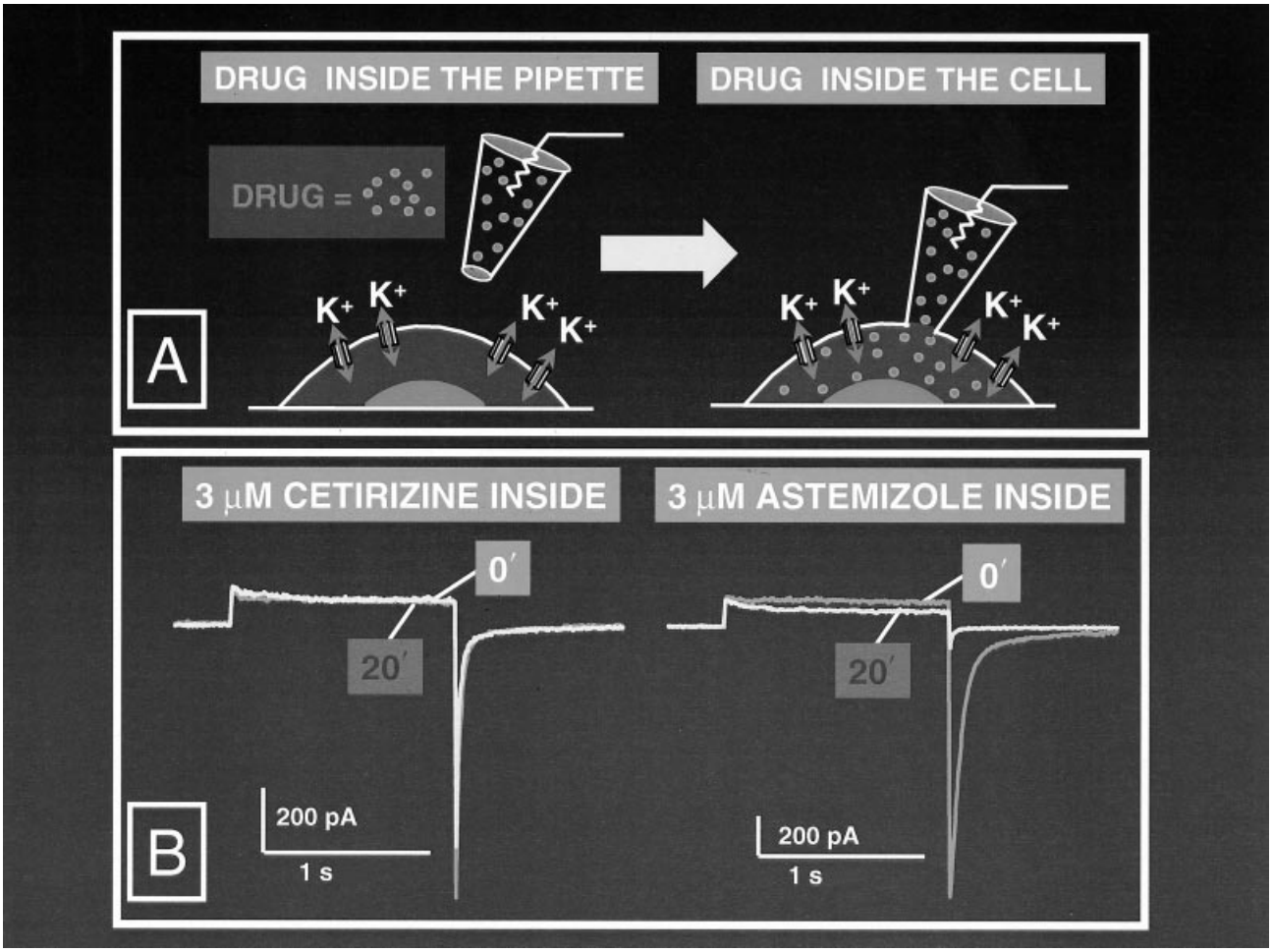

Figure 4. Effect of intracellular application of astemizole and cetirizine on hERG K^+ channels heterologously expressed in HEK 293 cells. A) Experimental setup for use of whole-cell configuration of patch-clamp technique to investigate effects of intracellular application of drugs. B) Two traces are shown from each of two HEK 293 cells: one in which pipette contained 3 μM cetirizine (left) and one in which pipette contained 3 μM astemizole (right). Traces were recorded in both cells immediately after breaking into cells (time 0) after 20 min of recordings (time 20). Efficient diffusion of drugs from pipette into cell cytoplasm was demonstrated by virtually complete suppression of IhERG in cell exposed intracellularly to astemizole.

anterior pituitary hormones, and are triggered by the opening of L-type voltage-sensitive calcium channels. Ca^{2+} fluxes can be measured by a very sensitive fluorescent probe (FURA-2) which changes its fluorescence emission in proportion to the intracellular Ca^{2+} concentration. Second-generation antihistamines able to block hERG K^+ channels dose-dependently suppressed the intracellular Ca^{2+} oscillations in GH3 cells. On the other hand, a very large concentration of cetirizine (50 μM) did not induce any change of intracellualar Ca^{2+} concentration in GH3 cells. These data, although very preliminary, are interesting findings from the physiologic point of view, as they suggest that hERG potassium channels play a role in intracellular Ca^{2+} oscillations, an interference which is mediated by the role played by these channels in the control of the resting membrane potential, which, in turn, regulates the opening of voltage-sensitive calcium channels. The different ability of second-generation antihistamines to interfere with Ca^{2+} oscillations in GH3 cells suggests that those drugs able to inhibit hERG K^+ channels might influence hormonal release from these cells, a possibility which is currently being tested.

Conclusions

The data summarized in this paper provide firm evidence that there is a difference between second-generation antihistamines in their ability to interfere with the potassium channel underlying the cardiac repolarizing current. It is therefore tempting to speculate that this might explain the different abilities of second-generation antihistamines to induce cardiotoxicity. Moreover, the techniques described here might provide useful screening tools to prevent the development of antihistamines with the potential to cause adverse cardiac effects. In conclusion, potassium channel blockade is not a class property of second-

generation antihistamines, and the described differences in the pharmacologic profile for several congeners belonging to this therapeutic class at the level of the hERG K^+ channels might provide important molecular evidence for the recognized differences in their propensity to cause serious cardiotoxic effects.

Discussion

Tharp: I guess these models are extremely sophisticated and very intriguing, but do they really reflect what we might see in an actual cardiomyocyte?

Taglialatela: Yes, we do believe that is the case. However, it is difficult to make direct comparisons because of the technical difficulties involved in isolating human ventricular myocytes. This is because they are very difficult cells to maintain in culture. Some investigators have used guinea-pig ventricular myocytes to look at astemizole, which blocked IKr in these cells. Of course, we don't know yet whether hERG is the only subunit making up the IKr channel; there could be others which are associated, but the general pharmacologic profile and the biophysical profile are likely to be very similar. Besides that, I must also mention that it's very difficult to isolate IKr because it's one of eight families of K^+ channels expressed in the same ventricular myocyte.

Knol: As part of the ETAC study, we performed ECGs in about 600 of the 815 children and could find no arrhythmias and no QT abnormalities in the cetirizine or placebo group.

Sake: You demonstrated an effect on the potassium channels by 3 μmol loratadine. Have you got a tentative explanation for this? Is it the substance itself, or is it the impact on the metabolism?

Taglialatela: I tend to think that metabolism in this system has very little effect because these are rapid events, occurring after 5–10 min of perfusion, either inside or outside; the longest we've gone is to 20 min of application on the inside. So I think that in these experimental systems we are looking at the effects of the parental molecules rather than those of the metabolites.

Donnelly: It's clear from this presentation that astemizole and terfenadine are the main molecular actors as far as this cardiotoxicity problem is concerned, and what we have seen with loratadine is that it seems to occupy an intermediate position, with similar phenomena being noted at much higher concentrations. Now, in reality, you may have drug interaction problems, you may have impaired hepatic metabolism; with that as a clinical backdrop, do you think that there is a question mark over loratadine?

Taglialatela: As already stated, it is difficult to translate these *in vitro* data into clinical situations. With regard to loratadine, if you look, for example, at the studies that have been presented by Prof. Annunziato on the effects of second-generation molecules on norepinephrine release, you will notice that the difference between astemizole, terfenadine, and loratadine is that loratadine now stands more with the devils than with the good guys. I tend to think that loratadine has a quite complex membrane permeability; for example, for loratadine, the difference between the oocyte system and the neuroblastoma cell system is very evident. In the oocyte, you have to increase the concentration to 30 μmol to see an effect; in the neuroblast cells, an inhibitory effect is seen with 3 or 1 μmol. It is not as pronounced as with terfenadine or astemizole, but it's observable.

Annunziato: I would like just to make a response to Dr Donnelly's question. I think that first of all in the data that Dr Taglialatela presented he got inhibition in SH-SY5Y cells at 3 μmol loratadine, a concentration which is at least 10 times higher than those reached *in vivo* in therapeutic settings. Therefore, loratadine could potentially exert cardiotoxic effects only in an overdose situation or if its liver metabolism is compromised. If we are to call them devils, we have to make the difference clear. So, I would underline that, for loratadine, there is still a large margin of safety, and this crucial consideration must be taken into account.

Donnelly: I was thinking more of situations that can occur in the street as opposed to in the clinical study, and this is something that we have to be aware of.

De Vos: Yes. Moreover, when you give loratadine with ketoconazole, the drug concentration of unchanged loratadine is considerably increased, so I think that we have to take this into account. Also, we don't know the true concentration of loratadine in the tissue itself due to the large volume of distribution or to the retention of the organ. It might be possible to reach these concentrations *in vivo* in certain situations.

Annunziato: To give a definite answer to your question, I think that it is very important to know if there are clinical studies showing the extent of increase of loratadine or astemizole levels in the presence of macrolides or antifungal drugs.

De Vos: Being from UCB, I would like to be devil's advocate. In the last model you showed us with the calcium oscillation, if I am right, you showed some data with terfenadine and astemizole with a time course of 1–200 s?

Annunziato: No, it was a 1000-s observation.

De Vos: Yes, but for cetirizine you stopped at 1000 s.

Annunziato: The differences in the acquisition times did not influence the results I have presented. Cetirizine, even after longer incubation times, was still ineffective in interfering with Ca^{2+} oscillations in GH3 cells.

Rihoux: Coming back to the issue of physiologic concentrations, we used microdialysis fibers to measure the level of cetirizine in the skin and found there was about 300 ng in the plasma and about 3 ng in the tissue

fluid. So I think that when we speak about therapeutic concentrations, it depends on whether we are talking about blood or the tissues. If we test neutrophils, the plasma concentrations are more important since neutrophils are circulating cells. In the microdialysis fluid, it is different; in the tissues, it could be less. But if a drug has a very high volume of distribution it could be exactly the opposite, so I think it is very difficult when we compare such concentrations.

Annunziato: Of course, you cannot make direct comparison between *in vitro* and *in vivo* studies. When we compared the concentrations used in our *in vitro* models with those observed in pharmacokinetic studies of H_1-receptor blockers in humans, particularly those during cardiac adverse effects, we found a pretty good correlation between the concentrations measured *in vivo* and those that were shown to block hERG potassium channels *in vitro*. Therefore, in these *in vitro* models, the drug concentration can be kept stable for seconds or minutes, allowing electrophysiologic studies of membrane ionic channels.

Rihoux: In animal models, we found that plasma cetirizine concentrations up to 80 times higher than those considered therapeutic had no effect on the ECGs of the animals.

Frossard: I was just wondering whether a low dose over time of astemizole or loratadine, which does not induce any effect in the short term, might have an effect over a longer period of time.

Taglialatela: We have never specifically tested that, but from experience of recording data we know that, for example, the dose response for terfenadine and astemizole was non-steady state, meaning that if instead of taking the points at 5 min we had waited for 8–10 min the dose response would have shifted to the left. That's because more of the drug would have accumulated inside the cells. So, to go back to your idea, if we had applied a lower dose of terfenadine or astemizole which was noneffective at 5 min and waited for 2 h, it seems likely that this concentration also would have been ineffective.

Annunziato: I wanted to make a final comment concerning the catecholamine release blocked by these H_1-receptor blockers. I would mention that there is evidence that isoproterenol and epinephrine, by virtue of their positive chronotropic actions, can help in preventing drug-induced long QT syndrome. Presumably this prolonged QT interval can happen in patients who have bradycardia, and who are therefore more likely to have torsade de pointes, and in this situation we could assume that epinephrine release could help increase the frequency of the heartbeat. Therefore, using these analogies, we can say that if an H_1-receptor blocker prevents endogenous catecholamine release by blocking hERG K^+ channels, this could precipitate the arrhythmia.

Acknowledgments

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