Antagonism by Class I Antiarrhythmic Drugs of Levocromakalim-Induced Relaxation in Isolated Rat Aorta

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ABSTRACT

We have analyzed the effects of several class I antiarrhythmic drugs (propafenone, quinidine, its enantiomer quinine, disopyramide, flecainide and mexiletine), tetraethylammonium (TEA) and glibenclamide on the vasodilator effects of the adenosine 5'-triphosphate-dependent K⁺ channels channel opener levocromakalim in isolated rat aorta precontracted by 30 mM KCl. TEA (>1 mM) and disopyramide (>10 μM) induced a sustained contraction in resting aortic rings. Propafenone (>3 mM), quinidine (>30 μM), disopyramide (>100 μM) and flecainide (>100 μM) but not the other drugs decreased the contraction induced by 30 mM KCl in a concentration-dependent manner. Propafenone (>1 μM), quinidine (>10 μM), quinine (>1 μM), disopyramide (>3 mM), flecainide (>100 μM), mexiletine (>3 mM), TEA (>0.3 mM) and glibenclamide (>0.1 μM) caused a concentration-dependent inhibition of the vasodilation induced by levocromakalim in rat aortic rings. The order of potency of the drugs, expressed as pD₂ values, to inhibit the vasodilation induced by 0.3 μM levocromakalim was the following: glibenclamide (6.84) > quinine (6.14) > propafenone (5.27) > disopyramide (5.03) > quinidine (4.80) > mexiletine (4.68) > flecainide (3.37) > TEA (3.20). With the exception of flecainide and mexiletine, the slopes of the Schild plots were similar to unity. Based on the mode of antagonism these drugs could be classified in four groups: 1) glibenclamide which only shifted the curves to the right, 2) quinidine and disopyramide that, at low concentrations, shifted the curve to the right but, at higher concentrations, it also reduced the maximal relaxant effect, 3) propafenone, quinine and TEA that shifted the curve rightwards and reduced the maximal relaxation at all concentrations and 4) flecainide and mexiletine whose Schild slopes were clearly different from unity. In conclusion, class I antiarrhythmic drugs inhibited levocromakalim-induced relaxation in isolated rat aorta. The concentrations at which these effects were observed were within the therapeutic range (except for flecainide) and similar to those reported to inhibit adenosine 5'-triphosphate-dependent K⁺ channel currents. Analysis of the concentration-response curves revealed that these drugs produced a noncompetitive antagonism of levocromakalim-induced relaxations.

KₐTP are expressed in a wide variety of cell types and regulate important cellular activities such as insulin secretion in pancreatic β cells, smooth muscle tone and repolarization of the cardiac action potential (Ashcroft and Ashcroft, 1990). These channels are specifically inhibited by physiological cytosolic ATP concentrations or by sulphonylurea drugs such as glibenclamide and are activated by KₐTP channel openers (Edwards and Weston, 1993). In vascular smooth muscle cells, activation of KₐTP channels hyperpolarize the cell membrane and reduce Ca²⁺ channel activity decreasing vascular tone (Quast, 1993; Edwards and Weston, 1995). Therefore, KₐTP channel openers are powerful vasodilators, levocromakalim being the most representative agent of this group.

Class I antiarrhythmic drugs include those agents that block cardiac Na⁺ channels, decreasing the rate of depolarization of cardiac cells (Tamargo et al., 1992). According to the rate of binding-dissociation from Na⁺ channels, class I drugs have been further classified into three subgroups: Ia, Ib and Ic (Vaughan Williams, 1984). However, most of the currently available class I drugs exhibit multiple actions, so that they can inhibit several other cardiac Ca²⁺ and K⁺ channels, thus, exerting also class III and class IV antiarrhythmic actions (Salata and Wasserstrom, 1988; Kotake et al., 1988; Scamps et al., 1989; Tamargo et al., 1992; Delgado et al., 1993; Slawsky and Castle, 1994; Delpón et al., 1995). In vascular smooth muscle, these drugs also inhibit Ca²⁺ entry through L-type Ca²⁺ channels leading to vascular smooth muscle relaxation (Carrón et al., 1991; Pérez-Vizcaíno et al., 1991, 1994; Fernández del Pozo et al., 1996, 1997).

A wide range of antiarrhythmic drugs has been reported to inhibit glibenclamide-sensitive currents activated by KₐTP channel openers in Xenopus oocytes (Sakuta et al., 1992). In addition, an inhibitory effect of some class I antiarrhythmic drugs (disopyramide, quinidine and its enantiomer quinine)
Materials and Methods

**Tissue preparation.** Male Wistar rats (300–350 g), were killed by a blow on the head and then exsanguinated. The descending thoracic aorta was rapidly dissected and placed in Krebs solution of the following composition (in mM): NaCl 118, KCl 5, NaHCO3 25, MgSO4 1.2, CaCl2 2, KH2PO4 1.2 and glucose 11 at pH 7.4. After excess of fat and connective tissue had been removed, the aorta was cut into rings (2–3 mm) and endothelium was mechanically removed by gently rubbing the intimal surface of the rings with a metal rod. The rings were suspended horizontally by means of two parallel L-shaped stainless steel holders inserted into the lumen in 5-ml organ baths filled with Krebs and bubbled with a 95% O2-5% CO2 gas mixture and maintained at 37°C. One holder served as anchor and the other was attached to an isometric force-displacement transducer coupled to a signal amplifier (Model PRE 206-4, Cibertec, Madrid, Spain) and connected to a computer via an A/D interface. Contractile force was recorded by a REGXCPC computer program (Cibertec) as previously described (Pérez-Vizcaíno et al., 1997). Each ring was stretched to a resting tension of 2 × g and allowed to equilibrate for 60 to 90 min. During this period tissues were re-stretched and washed every 30 min with warm Krebs solution. The procedure of endothelium removal was tested by the lack of relaxant effects of 10−6 M acetylcholine in rings precontracted with 10−6 M noradrenaline.

**Experimental procedures.** After equilibration, aortic rings were initially contracted by 30 mM KCl and when the tonic contractile response was stable, they were washed with Krebs solution to recover the basal tone. Rings were then exposed for 30 min to vehicle or the following drugs: propafenone (1, 3 and 10 μM), quinidine (3, 10, 30 and 100 μM), quinine (0.3, 1, 3 and 30 mM), disopyramide (3, 10, 30 and 100 μM), flecainide (10, 30 and 100 μM), mexiletine (1, 3, 10, 30 and 100 μM), TEA (0.1, 0.3, 1 and 3 mM) and glibenclamide (0.1, 0.3, 1 and 3 μM). Thereafter, a second contraction was induced by 30 mM KCl and a concentration-response relaxation curve was obtained by cumulative addition of levcromakalim (0.01–10 μM) in the continuous presence of the drugs. The relaxant response to levcromakalim in treated arteries was expressed as a percentage of the maximal response to levcromakalim in control arteries obtained in parallel experiments for each drug.

**Drugs.** The following drugs were used: quinidine sulfate, quinine hydrochloride, disopyramide phosphate, glibenclamide, tetraethylammonium chloride, acetylcholine chloride, noradrenaline (Sigma Chemical, Madrid, Spain), flecainide acetate (Laboratorios Dr. Esteve S.A. Barcelona, Spain), propafenone hydrochloride (Knoll AG Ludwigshafen, Germany), mexiletine (Boheringer Ingelheim) and levcromakalim (Smith Kline Beecham Pharmaceuticals Betchworth, U.K.). All drugs were dissolved in distilled deionized water to prepare a 10−2 or 10−3 M stock solution except glibenclamide that was dissolved in DMSO) and further dilutions were made in Krebs solution. The final concentration of DMSO used (≤0.01%) had no effect on the assays performed. Quinidine sulfate contains 2 mol of quinidine base per mol but the concentrations were expressed as final quinidine base concentrations.

**Analysis of the results.** Results are expressed as means ± S.E. of measurements in arteries from n different animals. Contractile responses are expressed as a percentage of the initial response to 30 mM KCl. Individual cumulative concentration-response curves were fitted to a logistic equation. The drug concentration exhibiting 50% of the maximal effect (E50) was calculated from the fitted concentration-response curves for each ring and expressed as negative log molar (pD2). The concentration-response curves to levcromakalim in the presence and absence of the drugs were analyzed by plotting the negative logarithm of the ratio of concentrations of the agonist that produced the same effect (50% relaxation) in the presence and absence of the antagonist minus 1 (log [concentration ratio – 1]) against the negative logarithm of the concentration of antagonist (i.e., Schild-plot analysis, Arunlakshana and Schild, 1959). The intercept on the abscissa yields the pA2 value (negative logarithm of the concentration of antagonist which induces a 2-fold rightward of the concentration-response to the agonist) which is an indicator of the affinity of the antagonist. The slope of this plot is an indicator of the type of antagonism, i.e., a slope similar to 1 is considered to be competitive antagonism. Statistically significant differences were calculated by a two-way analysis of variance analysis. P < .05 was considered statistically significant.

**Results**

**Effects on basal tension.** At the range of concentrations tested, propafenone, quinidine, flecainide, mexiletine and glibenclamide did not produce any significant change in basal tension. A transient contraction was occasionally observed with 100 μM quinidine or 1 mM TEA but the final tone after 30 min of exposure to the drug was not significantly different from the basal value. TEA (3 mM) and disopyramide (≥10 μM) induced a sustained contraction representing 66 ± 18% (n = 7) and 48 ± 4% (n = 6) of the contraction induced by 30 mM KCl, for 3 mM TEA and 100 μM disopyramide, respectively.

**Effects on KCl-induced contraction.** Rings were initially contracted by 30 mM KCl (1052 ± 33 mg, n = 219), then washed in normal Krebs solution, exposed to vehicle or different concentrations of class I drugs, TEA or glibenclamide for 30 min and again exposed to 30 mM KCl. The contractile response to 30 mM KCl after exposure to vehicle in control rings averaged 107 ± 2% of the initial contraction (n = 43). Propafenone (≥3 μM), quinidine (≥30 μM), disopyramide (≥100 μM) and flecainide (≥100 μM) significantly decreased the degree of contraction induced by 30 mM KCl in a concentration-dependent manner as compared to controls (76 ± 6 and 44 ± 3% at 3 and 10 μM propafenone, respectively; 84 ± 2 and 46 ± 2% at 30 and 100 μM quinidine, respectively; 85 ± 3% at 100 μM disopyramide and 44 ± 5% at 100 μM flecainide, P < .05, n = 5–8). In contrast, at the range of concentrations tested, quinidine, mexiletine, TEA and glibenclamide had no effect on the 30 mM KCl-induced contraction.

**Effects on levcromakalim-induced relaxation.** Levcromakalim (0.01–10 μM) induced a concentration-dependent relaxation in control arteries precontracted by 30 mM KCl (pD2 = 7.04 ± 0.02, Emax = 85 ± 2%, n = 43). Propafenone (1, 3 and 10 μM), quinidine (3, 10, 30 and 100
μM), quinine (0.3, 1, 3, 10 and 30 μM), disopyramide (3, 10, 30 and 100 μM), flecainide (10, 30 and 100 μM), mexiletine (1, 3, 10, 30 and 100 μM), TEA (0.1, 0.3, 1 and 3 mM) and glibenclamide (0.1, 0.3 and 1 μM) caused a concentration-dependent inhibition of the vasodilation induced by levocromakalim in rat aortic rings (fig. 1). All these agents shifted the concentration-response curve to the right, decreasing the pD₂ value for levocromakalim-induced relaxation. This effect reached statistical significance for all concentrations tested of propafenone, disopyramide and glibenclamide, and for concentrations ≥10 μM quinidine, ≥1 μM quinine, ≥100 μM flecainide, ≥3 μM mexiletine and ≥0.3 mM TEA. The E₅₀ for levocromakalim was not significantly different in aortic rings treated with glibenclamide, flecainide or with the low concentrations of quinidine (3, 10 and 30 μM), disopyramide (3 and 10 μM), mexiletine (1 μM) or TEA (0.1 mM) as compared to controls, whereas propafenone, quinine and higher concentrations of quinidine, disopyramide, mexiletine and

![Fig. 1. Antagonism by class I antiarrhythmic drugs (A–F), TEA (G) and glibenclamide (H) of the relaxant response to levocromakalim. Concentration-response curves to levocromakalim were carried out in arteries pre-contracted by 30 mM KCl in the absence (controls □) or in the presence of propafenone, quinidine, quinine, disopyramide, flecainide, mexiletine, TEA or glibenclamide. Each symbol represents the mean ± S.E. of five to nine experiments. Results are expressed as a percent of the maximal relaxation in control experiments.](https://www.aspetjournals.org/content/83/1/1998.full)
TEA significantly decreased the $E_{\text{max}}$. The $E_{\text{max}}$ reduction induced by these drugs was concentration-dependent except for mexiletine which induced a similar reduction at concentrations between 3 and 100 $\mu$M.

The inhibitory effect of these drugs on the relaxation induced by 0.3 $\mu$M levcromakalim (a submaximally effective concentration) is plotted in figure 2. The order of potency of the drugs for this inhibitory action expressed as pD2 values was the following: glibenclamide (6.84), quinine (6.14), propafenone (5.27), disopyramide (5.03), quinidine (4.80), mexiletine (4.51), flecainide (3.37) and TEA (3.20). Therefore, quinidine was about 20 times less potent than its enantiomer quinine.

The Schild plot for the inhibitory action on levcromakalim-induced relaxation is shown in figure 3. The slopes of these plots yielded values of 1.06 for propafenone, 0.96 for quinidine, 0.82 for quinine, 0.89 for disopyramide, 0.51 for flecainide, 0.41 for mexiletine, 0.84 for TEA and 1.06 for glibenclamide. Therefore, with the exception of flecainide and mexiletine, these slopes were similar to unity. The pA2 values calculated from the Schild plot were 5.58 for propafenone, 5.20 for quinidine, 6.21 for quinine, 5.64 for disopyramide, 4.05 for flecainide, 4.93 for mexiletine, 3.54 for TEA and 7.06 for glibenclamide.

**Discussion**

We have analyzed the antagonism of several class I antiarrhythmics on the relaxation induced by the KATP channel opener levcromakalim in the isolated rat aorta. The results were compared to those of the specific KATP inhibitor glibenclamide and the nonselective K+ channel blocker TEA. All the drugs tested (i.e., propafenone, quinidine, quinine, disopyramide, mexiletine and flecainide) inhibited the relaxations induced by levcromakalim in a concentration-dependent manner. The order of potency for this inhibitory action was the following: glibenclamide, quinine, propafenone, disopyramide, quinidine, mexiletine, flecainide and TEA. All drugs, produced a rightward shift of the concentration-response curve to levcromakalim, and with the exception of glibenclamide, they also reduced its maximal relaxant response.

TEA and disopyramide produced a sustained contraction under basal tension. This effect may be attributable to the blockade of the K+ channels involved in the control of resting membrane potential leading to depolarization of vascular smooth muscle cells which, in turn, opens L-type Ca++ channels (Bolton, 1979). However, despite the contraction induced by TEA and disopyramide the tone after the subsequent addition of KCl was not greater than that in the absence of these drugs, i.e., TEA- and disopyramide-induced contractions were not additive to the KCl-induced contraction. Propafenone, quinidine, disopyramide and flecainide (but not the other drugs) decreased the contractions induced by 30 mM KCl. The order of potency for this effect was the following: propafenone, quinidine, disopyramide and flecainide. This inhibitory action on 30 mM KCl-induced contractions is consistent with our previous reports showing that these drugs inhibit the contractions and 45Ca++ entry induced by high (80 mM) KCl concentrations due to their L-type Ca++ channel blocking properties (Carrón et al., 1991; Pérez-Vizcaíno et al., 1991, 1994; Fernández del Pozo et al., 1996, 1997). Furthermore, they confirm the stereoselectivity of quinidine-induced inhibition (Fernández del Pozo et al., 1996). This inhibition of Ca++ entry limited the use of higher concentrations of some drugs such as flecainide, which at 100 $\mu$M inhibited the contraction induced by 30 mM KCl by about 50% and only had a weak inhibitory action on levcromakalim-induced relaxation. However, the inhibitory action of levcromakalim-induced relaxation seems to be independent on the inhibition of KCl-induced contractions since the order of potency of both effects was different (e.g., the stereoselectivity of quinidine-induced inhibition for both effects was opposite).

The inhibitory effects on KATP channels have been reported for disopyramide in cat ventricular myocytes (De Lorenzi et al., 1995) and mouse skeletal muscle (Moser et al., 1995), for quinidine in cat ventricular myocytes (De Lorenzi et al., 1995) and for quinine in pancreatic $\beta$ cells (Bovkist et al., 1990). The actions of a wide range of antiarrhythmics (including propafenone, quinidine, disopyramide, flecainide and mexiletine) on the K+ current induced by K+ channel open-
ers have also been studied in Xenopus oocytes (Sakuta et al., 1992). It has been reported that $K_{ATP}$ channels in Xenopus follicular cells and in vascular smooth muscle cells share common biophysical, pharmacological and regulation properties (Guillemande et al., 1995). The order of potency reported in Xenopus oocytes (calculated $pD_2$ values of 6.52 for glibenclamide, 4.75 for disopyramide, 4.2 for propafenone, 3.82 for quinidine and 3.35 for flecainide, Sakuta et al., 1992) was very similar to that reported in our study. In fact, although our $pD_2$ values were slightly greater than those reported by Sakuta et al. (1992), we found a very good correlation between the $pD_2$ values of both studies (correlation coefficient of 0.93 and a slope of 0.94, $P < .05$). Furthermore, our results indicate that the degree of inhibition by class I antiarrhythmics is a function of the concentration of $K_{ATP}$ channel opener used because they behave, at least over a certain range of concentrations, as apparent competitive antagonists. The results obtained with mexiletine are difficult to compare with other studies, because it has been reported to be both an inhibitor ($pD_2 = 2.89$ in Xenopus oocytes; Sakuta et al., 1992) and an activator of $K_{ATP}$ channels (in guinea pig papillary muscles; Sato et al., 1995). The potency of quinine in our study was also consistent with that reported by Bovkist et al. (1990) in pancreatic $\beta$ cells. Therefore, the inhibitory effect of class I antiarrhythmic drugs observed in our study on levcromakalim-induced relaxation paralleled that found on $K_{ATP}$ channel opener-induced $K^+$ currents by other authors.

In our study, glibenclamide shifted the concentration-response curves to levcromakalim to the right without affecting the maximal relaxant response and the Schild plot analysis yielded slope values similar to unity, indicating an apparent competitive antagonism. Quinidine and disopyramide, at low concentrations, reduced the $pD_2$ value without affecting the $E_{max}$ of levcromakalim, whereas at higher concentrations they reduced both parameters. Propafenone, quinidine and TEA at concentrations that induced a weak reduction in the $pD_2$ value significantly decreased the $E_{max}$. Therefore, despite the fact that the slope of the Schild plot was similar to unity, the antagonism induced by these drugs cannot be considered as competitive. Flecainide produced a weak inhibitory action which was observed only at concentrations that produced a marked inhibition of KCl-induced contraction. Mexiletine reduced both the $pD_2$ value and the $E_{max}$; however, its inhibitory action did not show a clear concentration dependency because it induced a similar reduction at concentrations between 3 and 100 $\mu$M. This effect might be related to its dual action on $K_{ATP}$ channels, because it has been reported to be an inhibitor in Xenopus oocytes (Sakuta et al., 1992) and an activator in guinea pig papillary muscles (Sato et al., 1995).

$K_{ATP}$ channel is a multimeric complex of inwardly rectifying $K^+$ channel subunits (Kir 6.1 or Kir 6.2) and the sulphonylurea receptor (SUR1 or SUR2) (Inagaki et al., 1995). Glibenclamide interacts at a specific binding site in SUR1 that is not located in the pore region of the channel. In functional studies, glibenclamide behaves as an apparent competitive antagonist of levcromakalim and other related $K_{ATP}$ channel openers (Pérez-Vízcaíno et al., 1993; Edwards and Weston, 1993) but as shown in binding studies, $K_{ATP}$ channel openers (with the exception of diazoxide) do not compete with glibenclamide for its binding site (Gopalakrishnan et al., 1991), indicating that the glibenclamide site is different from, but negatively allosterically coupled to the binding site for the openers (Bray and Quast, 1992). In contrast, the nonselective $K^+$ channel blockers TEA and antiarrhythmic drugs are thought to inhibit $K^+$ currents by binding to the pore region of the channel (Yellen et al., 1991; Kirsch et al., 1991; Snyders and Yeola, 1995) and at the concentrations at which inhibit levcromakalim-induced relaxation, quinidine, quinidine and TEA had no effect on [$^3$H]-glibenclamide binding (Go-palakrishnan et al., 1991). However, it is not known whether these drugs can bind to the $K_{ATP}$ channel opener site. Furthermore, the inhibitory action of antiarrhythmic drugs on $K_{ATP}$ currents has been correlated with their ability to bind calmodulin, suggesting the existence of a calmodulin-like structure associated with the $K_{ATP}$ channel (Sakuta et al., 1992). Thus, several targets related to the $K_{ATP}$ channel might be responsible for the inhibition of levcromakalim-induced relaxation. However, an interaction of class I drugs with other targets different from the $K_{ATP}$ channel that may indirectly affect levcromakalim-induced relaxation cannot be completely ruled out from our experiments. The different interaction of glibenclamide, TEA and class I antiarrhythmic drugs with these targets may explain their distinct mode of antagonism on levcromakalim-induced relaxation.

It is interesting to note that, with the exception of flecainide, the concentrations of class I antiarrhythmic drugs which significantly inhibited levcromakalim-induced relaxation in our study were within the therapeutic range used for the treatment of cardiac arrhythmias (therapeutic range: 0.92–5 $\mu$M for propafenone, 6–15 $\mu$M for quinidine, 8–22 $\mu$M for disopyramide, 0.5–2 $\mu$M for flecainide and 2.8–11 $\mu$M for mexiletine; Roden, 1996). Thus, it may be possible that the inhibitory action on $K_{ATP}$ channels is clinically relevant during the course of arrhythmia treatment with class I antiarrhythmic drugs. Under physiological conditions, $K_{ATP}$ channels are not basally activated in most vascular beds and, therefore, their inhibition does not result in vasoconstriction. In fact, glibenclamide has no effect on arterial blood pressure (Edwards and Weston, 1995). However, $K_{ATP}$ channels regulate arterial tone in several vascular beds, namely the coronary circulation where their blockade results in significant vasoconstriction (Samaha et al., 1992). Moreover, hypoxic vasodilation in isolated perfused hearts can be blocked by glibenclamide and mimicked by cromakalim (Daut et al., 1990). These results suggest that opening of $K_{ATP}$ channels appears to be a major physiological way of achieving coronary vasodilation (Richer et al., 1990). In our study, we found that class I antiarrhythmic drugs block $K_{ATP}$ channel-mediated vasorelaxation. So that it would be expected that any pathophysiological role of $K_{ATP}$ channels in vascular smooth muscle tone might be inhibited by these drugs. The routine use of class I antiarrhythmic drugs after myocardial infarction is associated with increased mortality (Teo et al., 1993). One working hypothesis to explain increased mortality is that class I drugs exert a deleterious effect on ischaemic myocardium (Eth et al., 1991; Podrid and Fogel, 1992). In fact, in animal models class I antiarrhythmics have a proarrhythmic potential when combined with acute ischaemia, a condition where $K_{ATP}$ channels are maximally activated (Elharrar et al., 1977; Nattel et al., 1981). From our data it could be speculated that $K_{ATP}$ channel blockade by class I antiarrhythmics might increase coronary tone and inhibit hypoxia...
induced coronary vasodilation, thus increasing ischemia. This effect together with the slowing of intracardiac conduction may convert a stable myocardium into an unstable and arrhythmogenic one (Podrid and Fogel, 1992). However, we must keep in mind that class I antiarrhythmic agents exert multiple effects including calcium channel blocking properties that may partially counteract the effect of blocking $K_{ATP}$ channels. Therefore, the net final effect would be different depending on the drug and the experimental conditions.

In conclusion, the class I antiarrhythmic drugs (propafenone, quinidine, quinidine, disopyramide, flecainide and mexiletine) inhibited levcromakalim-induced relaxation in isolated rat aorta. The concentrations at which these effects were observed were within the therapeutic range and similar to those reported in inhibited levcromakalim-induced relaxation in isolated rat myocardium and quinine, disopyramide, flecainide and mexiletine). Therefore, the net final effect would be different depending on the drug and the experimental conditions.

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References

Bray K and Quast U (1991) Tetradismal (KC 8857) differentially inhibits the 86Rb+ to inhibit KATP currents. Analysis of the concentration-response curves revealed that these drugs produced a noncompetitive antagonism of levcromakalim-induced relaxations.