Electrophysiological Effects of Prucalopride, a Novel Enteroactive Agent, on Isolated Atrial Myocytes from Patients Treated with β-Adrenoceptor Antagonists

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ABSTRACT

Prucalopride is a selective 5-hydroxytryptamine type 4 (5-HT₄) receptor agonist developed for the treatment of gastrointestinal disorders. The endogenous agonist 5-HT acting via 5-HT₄ receptors increases the L-type Ca²⁺ current (I_{CaL}) with potentially proarrhythmic consequences (Pau et al., 2003). The aims of this study were to investigate the effects of prucalopride on I_{CaL}, action potentials, refractory period, and arrhythmic activity in human atrial myocytes, and to compare these with the effects of 5-HT, using the whole-cell perforated patch-clamp technique. Prucalopride (10⁻³ to 10⁻¹ M) produced a concentration-dependent increase in I_{CaL} amplitude, with a maximum response at 10 μM, from −5.3 ± 0.6 to −10.9 ± 1.5 pA/pF (p < 0.05; n = 22 cells, 10 patients), without affecting its voltage-dependence. Subsequent application of 10 μM 5-HT further increased I_{CaL} to −17.7 ± 2.8 pA/pF (p < 0.05; n = 16 cells, 9 patients). The increase in I_{CaL} by prucalopride, 98 ± 15%, was significantly smaller than that by 5-HT, 233 ± 26% (p < 0.05). Prucalopride (10 μM) significantly increased the action potential duration at 50% repolarization (APD_{50}) from 12 ± 2 to 17 ± 3 ms (p < 0.05; n = 22 cells, 9 patients). Following washout of prucalopride, 5-HT (10 μM) increased APD_{50}, to a greater extent, from 14 ± 3 to 32 ± 7 ms (p < 0.05; n = 11 cells, 8 patients). The APD_{75}, APD_{90}, and effective refractory period were unaffected by prucalopride or 5-HT. Furthermore, 5-HT induced abnormal depolarizations in 27% of the cells studied, whereas prucalopride induced none (p < 0.05). In conclusion, in human atrial cells, prucalopride, at concentrations markedly above those used therapeutically, acted as partial agonist on I_{CaL} and APD_{50}, with no effect on late repolarization or refractory period, and was devoid of arrhythmic activity.

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ABBREVIATIONS: 5-HT₄, 5-hydroxytryptamine type 4; RS-100302, N-(2-[4-[3-(8-amino-7-chloro-2,3-dihydrobenzo[1,4]dioxin-5-yl)-3-oxo-propyl]-piperidin-1-yl]-ethyl)-methanesulfonamide; HERG, human ether-a-go-go-related gene; APD, action potential duration; ERP, effective refractory period; bpm, beat(s) per minute; GR-113808, [1-2-(methylsulfonlamino)ethyl]-4-piperidinyl]methyl 1-methyl-1H-indole-3-carboxylate.
Electrical Effects of Prucalopride in Human Atrial Myocytes

Materials and Methods

Tissue and Cell Isolation. Procedures for obtaining human tissue were approved by the institutional ethics committee of Glasgow Royal Infirmary and conform to the Declaration of Helsinki (World Medical Association, 1997). Samples of the right atrial appendage were obtained from consenting patients undergoing cardiac surgery. All patients had received prior therapy with β-adrenoceptor antagonists. Atrial cells were isolated enzymatically using a method described in detail by Workman et al. (2001).

Electrical Recording Techniques. The whole-cell perforated patch-clamp technique was used to record action potentials and calcium currents, as described in detail by Pau et al. (2003). Briefly, cells were superfused at 37°C with a physiological solution containing: 130.0 mM NaCl, 5.0 mM KCl, 2.0 mM CaCl2, 1.0 mM MgCl2, 10.0 mM glucose, and 4.0 mM HEPES, pH 7.4. To record calcium currents, electrodes were filled with a solution containing: 30.0 mM CsCl, 5.0 mM HEPES, 1.0 mM MgCl2, 100.0 mM K methanesulfonic acid, and 5.0 mM NaCl. To record action potentials, an internal solution containing 30.0 mM CsCl, 5.0 mM HEPES, 1.0 mM MgCl2, 100.0 mM Cs methanesulfonic acid, and 5.0 mM NaCl was used. To record action potentials, an internal solution containing 30.0 mM CsCl, 5.0 mM HEPES, 1.0 mM MgCl2, 100.0 mM Cs methanesulfonic acid, and 5.0 mM NaCl was used. The series resistance was observed to stabilize between 5 and 15 min at 9.9 mV (50% peak ICaL), action potentials, and the ERP were recorded before, and 90 s after, drug additions and again 180 s after removal of drugs.

Drugs. Prucalopride (R093877; Briejer et al., 2001) and the specific 5-HT4 antagonist GR-113808 (Kaumann, 1993) were donated by Johnson and Johnson Pharmaceutical Research and Development (Beere, Belgium) and were dissolved in dimethyl sulfoxide with a stock solution of 10 mM and subsequently diluted in physiological solutions. 5-HT (Sigma-Aldrich, St. Louis, MO) was made up as a 10 mM stock solution in distilled water.

Data Analysis and Statistics. Clinical characteristics and drug treatments of each patient were obtained from the case notes. Only patients in sinus rhythm at the time of surgery were included. Cells were excluded from analysis if either the APD50 or peak ICaL decreased irreversibly during the protocol. Concentration-response data for the effect of prucalopride on ICaL were fitted iteratively (Prism 3.0; GraphPad Software Inc., San Diego, CA) using a variable slope sigmoidal concentration-response curve (Hill equation). The curves were fitted to mean ICaL values, obtained at six concentrations of prucalopride between 1 nM and 100 μM. The concentration-response curve for 5-HT was obtained previously in our lab (Pau et al., 2003). Curve-fit values were compared using a two-tailed unpaired Student’s t test. Time-dependent inactivation of ICaL was fitted by a biphasional function using the WCP software program and was defined by the following equation: ICaL(t) = A1(e^(-t/τ1) + A2e^(-t/τ2) + C, where A1, A2, τ1, and τ2 are the amplitudes and decay time constants of the respective exponential components, and C is the steady-state amplitude. Data are expressed as mean ± S.E.M., with n being equal to the number of cells studied. Mean values were compared using two-tailed paired or unpaired Student’s t tests, as appropriate. A Fisher’s exact test was used to assess the level of significance of differences in the incidences of arrhythmic activity between drugs. p < 0.05 was regarded as statistically significant.

Results

Patients’ Clinical Characteristics. All patients were undergoing coronary artery bypass graft surgery, were taking β-adrenoceptor antagonists, suffered from angina, and none had severe left ventricular dysfunction (Table 1). Eighty-two percent of the patients were also treated with an angiotensin-converting enzyme inhibitor and 36% of the patients with a calcium channel blocker. β-Adrenoceptor antagonists had been administered for more than 10 days prior to surgery. No patient was administered sotalol (a β-blocker with additional class III antiarrhythmic activity). Patients received their routine cardiac drugs on the day of surgery. Mean heart rate was 58 ± 2 bpm (n = 11).

Effects of Prucalopride, 5-HT, and GR-113808 on ICaL in Human Atrial Cells. Prucalopride produced a significant increase in the amplitude of ICaL, as shown in Fig. 1 by the ICaL current density-voltage relationships. An example of original ICaL recordings is also shown (Fig. 1, inset). Prucalopride (10 μM) increased the mean magnitude of peak ICaL (recorded at +10 mV) from −5.7 ± 0.7 pA/pF to −10.2 ± 1.6 pA/pF (p < 0.05, n = 10 cells, 7 patients). This increase in peak ICaL occurred without any change in the voltage dependence of the current and was reversible on washout of prucalopride (−5.7 ± 1.1 pA/pF; n = 7 cells, 5 patients).

atrial arrhythmias via intracellular Ca2+ overload and/or a reduced refractoriness (Tonini et al., 1999; Yusuf et al., 2003).

Prucalopride, a novel 5-HT4 receptor agonist with a benzofuran-carboxamide structure, is currently under investigation for the treatment of idiopathic chronic constipation (Coremans et al., 2003). It has been demonstrated to be a potent and specific 5-HT4 receptor agonist in studies on human native and recombinant 5-HT4 receptor subtypes (Prins et al., 2000; Briejer et al., 2001; Pindon et al., 2002). There has been only one previous study on the effects of prucalopride on cardiac ion currents, specifically the rapid component of the recombinant delayed rectifier K+ current (IKr) encoded by the cloned human ether-a-go-go-related gene (HERG) (Potet et al., 2001). This study showed that micromolar concentrations of prucalopride significantly blocked IKr. Although IKr is present in the human ventricle (Li et al., 1996), in the human atrium it is not clear whether IKr may play a substantial role in action potential repolarization (Wang et al., 1994; Lee and Lee, 1998; Bertaso et al., 2002). The electrophysiological effects of prucalopride have not yet been studied in human atrium.

The aims of this study were to assess in human atrial myocytes the electrophysiological effects of prucalopride on ICaL, action potential duration (APD), cellular effective refractory period (ERP), and arrhythmic activity; and to compare the effects of prucalopride with those of the endogenous agonist 5-HT.

beats/min (bpm) using 5-ms stimulating pulses of 1.2× threshold strength. The ERP was measured using a standard S1-S2 stimulation protocol and was defined as the longest S1-S2 interval that failed to elicit an S2 action potential of amplitude >50% of the preceding S1 action potential. The APD was calculated as the interval between the action potential upstroke and repolarization to the level of 50% (APD50), 75% (APD75), and 90% (APD90) of the upstroke amplitude. ICaL, action potentials, and the ERP were recorded before, and 90 s after, drug additions and again 180 s after removal of drugs.

Effects of Prucalopride, 5-HT, and GR-113808 on ICaL in Human Atrial Cells. Prucalopride produced a significant increase in the amplitude of ICaL, as shown in Fig. 1 by the ICaL current density-voltage relationships. An example of original ICaL recordings is also shown (Fig. 1, inset). Prucalopride (10 μM) increased the mean magnitude of peak ICaL (recorded at +10 mV) from −5.7 ± 0.7 pA/pF to −10.2 ± 1.6 pA/pF (p < 0.05, n = 10 cells, 7 patients). This increase in peak ICaL occurred without any change in the voltage dependence of the current and was reversible on washout of prucalopride (−5.7 ± 1.1 pA/pF; n = 7 cells, 5 patients).
The concentration-response relationship of the effect of prucalopride on ICaL. The concentration-response curve of the effect of prucalopride on peak ICaL density (pA/pF) plotted at 5-s resolution, in response to 10 μM prucalopride (open box), followed by the application of GR-113808 at 1 μM (solid box), and the subsequent washout of the antagonist. Inset traces (a–d) show original currents recorded at the time points labeled.

The Concentration-Response Relationship of the Effect of Prucalopride on ICaL. The concentration-response curve of the effect of prucalopride on peak ICaL, obtained in atrial cells from patients with prior β-adrenoceptor antagonists treatment, is shown in Fig. 4. This figure also shows the superimposed concentration-response curve of the effect of 5-HT on peak ICaL, obtained previously in our lab in atrial cells from a similar group of patients (Pau et al., 2003). Prucalopride (from 1 nM to 100 μM) elicited a concentration-dependent increase in the amplitude of peak ICaL (measured at +10 mV), with a maximum response (Emax) equal to an increase of 93 ± 14% above control (n = 22–9

Table 1
Patients’ preoperative clinical characteristics
Values are numbers of patients (n) and percentage of total, respectively, with selected clinical characteristics, except for age (mean ± S.E.M.). All patients were in sinus rhythm on the day of surgery.

<table>
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<td>Age</td>
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| CABG, coronary artery bypass graft surgery; AVR, aortic valve replacement; ACE, angiotensin-converting enzyme; MI, myocardial infarction; LV, left ventricular.
patients). This was significantly less than that produced by the maximum response of 5-HT ($E_{\text{max}} = 299 \pm 12\%$ above control; $p < 0.05$). However, there were no significant differences between prucalopride and 5-HT for either the log EC$_{50}$ ($6.53 \pm 0.44$ versus $7.09 \pm 0.07$, respectively) or the Hill coefficient, $n_H$ ($0.76 \pm 0.46$ versus $1.46 \pm 0.56$, respectively).

**Effect of Prucalopride and 5-HT on Action Potentials and the Refractory Period.** Fig. 5 shows representative traces of action potentials and measurements of ERP illustrating the effects of 10 $\mu$M prucalopride (Fig. 5B) or 5-HT (Fig. 5C), compared with control conditions (Fig. 5A). Prucalopride (10 $\mu$M) caused a small but significant prolongation in the APD$_{50}$ from 12 to 17 ms ($p < 0.05$; $n = 22$ cells, 9 patients), representing an increase of 5 ms ($p < 0.05$). This effect was fully reversible upon washout of prucalopride (12 ± 3 ms; $n = 13$ cells, 8 patients). There was no significant or reversible effect of prucalopride on the APD$_{75}$, APD$_{90}$ or the ERP, consistent with our previous report (Pau et al., 2003). Figure 6B shows that the calcium channel blocker nifedipine at 10 $\mu$M prevented the prucalopride and the 5-HT-induced increases in APD$_{50}$ in the 11 (5 patients) and 4 (2 patients) cells studied, respectively. This concentration of nifedipine had been shown to markedly reduce I$_{\text{CaL}}$ from $-4.8 \pm 0.8$ to $-0.2 \pm 0.1$ pA/pF ($p < 0.05$; $n = 5$ cells, 4 patients).
Effects of Prucalopride and 5-HT on Arrhythmic Activity in Human Atrial Cells. Abnormal depolarizations were not observed in any of the 22 cells to which 10 μM prucalopride was applied. In contrast, when 10 μM 5-HT was subsequently applied (to 11 of these), abnormal depolarizations occurred in 3 (27%) of the cells studied (p < 0.05). Figure 7 shows an example of abnormal depolarizations caused by 5-HT, but not by prucalopride, and their abolition by GR-113808 at 1 μM. In another cell, from a different patient, 5-HT induced abnormal depolarizations in the absence, but not in the presence, of nifedipine at 10 μM (not shown).

Discussion

This study has demonstrated, for the first time to our knowledge, that prucalopride in human atrial cells acted as a partial rather than full agonist on the L-type calcium current and action potential early repolarization via 5-HT4 receptors. Similarly to 5-HT, prucalopride lacked effects on the late phase of the atrial action potential repolarization and the effective refractory period. Unlike 5-HT, prucalopride did not induce abnormal depolarizations.

Prucalopride has been shown previously to be a full agonist in several areas of the human body including the gastrointestinal (Prins et al., 2000) and central nervous (Robert et al., 2001) systems. Studies using either native or recombinant 5-HT4 receptors have shown that prucalopride had similar, or even greater, efficacy than the endogenous agonist 5-HT (Prins et al., 2000; Pindon et al., 2002; Lezoualc’h and Robert, 2003). The EC50 value for prucalopride in human atrial cells in the present study was higher than that obtained with human recombinant 5-HT4a and 5-HT4b receptor isoforms (Briejer et al., 2001; Pindon et al., 2002), which indicated a lower potency of the agonist in human atrial cells. In this study, we included only patients who had been previously treated with β-adrenoceptor antagonists. Such prior therapy did not affect the mRNA expression of 5-HT4 receptors and L-type Ca2+ channels subunits α1c, α2/β1, β1b, and β1c in the human atrium (Grammer et al., 2001). However, we have previously shown in human atrial cells that prior β-blockade enhanced the maximal response of ICaL to 5-HT but with no effect on the EC50 or the Hill coefficient of the concentration-response curve for 5-HT (Pau et al., 2003).
5-HT4 isoforms have been associated with different receptor levels of expression (Bach et al., 2001; Medhurst et al., 2001; Vilaro et al., 2002; Brattelid et al., 2004). Thus, it is possible that prucalopride acts as partial agonist with low potency in human atrial cells because of the expression of specific 5-HT4 isoforms and/or because of the different levels of expression of these isoforms present in the human atrium, compared with other tissues. In addition, 5-HT and prucalopride, acting via 5-HT4 receptors, may differently affect the signal transduction cascade, including the phosphorylation of different isoforms of the L-type Ca2+ channel (Pindon et al., 2002). These questions may be resolved following the development of more selective agonists, antagonists, and antibodies acting on specific 5-HT4 receptor subtypes or by coexpressing the L-type Ca2+ channels with the recombinant 5-HT4 receptors isoforms in a 5-HT receptor-free cell model.

Prucalopride significantly prolonged the early repolarization phase of the action potential without affecting the late phase or the refractory period, likely due to the observed increase in ICaL. This was confirmed by the experiments using the calcium channel blocker, nifedipine, which abolished the effects of prucalopride and 5-HT on the action potential. In addition, prucalopride had a less marked action to prolong APD50 than did 5-HT (at maximally effective concentrations), consistent with the partial activity observed on ICaL. However, we cannot exclude effects on other currents of importance during repolarization in the human atrium, such as the transient outward K⁺ current, Ito, and the ultra-rapid component of the delayed rectifier K⁺ current, IKur.

The fact that a 5-HT₄ antagonist, RS-100302, prolonged the ERP in an in vivo pig model of atrial fibrillation (Rahme et al., 1999) suggested that 5-HT₄ agonists may shorten the ERP and, therefore, be pro-arrhythmic by reducing the minimum path length required for re-entry. However, this is not supported by our experiments in isolated human atrial cells, in which neither prucalopride nor 5-HT abbreviated the late phase of repolarization or the refractory period. It is noteworthy that in canine atrial cells isolated using the chunk method, the repolarizing, delayed rectifier K⁺ current was recorded in significantly fewer cells than in those isolated by enzyme perfusion (Yue et al., 1996). Also, it has been reported that, in the human atrium, this current is limited to only a subpopulation of cells (Wang et al., 1994) or even absent (Lee and Lee, 1998; Bertaso et al., 2002). These two factors may explain the lack of effect of prucalopride and 5-HT to shorten late repolarization and refractory period in human atrial myocytes. Alternatively, in the pig, the 5-HT₄ antagonist, RS-100302, may have had a direct effect, independently of blocking 5-HT receptors to prolong ERP.

In the present study, we investigated the effects on ICaL of a range of concentrations of prucalopride, from 1 nM to 100 μM, to obtain a full concentration-response relationship of the drug. For comparison, the effective therapeutic range of prucalopride in humans has been found to be between 1 and 10 nM with a mean plasma concentration of around 2 ng/ml (~5 nM) after a 4-week treatment period and with a half-life of prucalopride around 24 h (Emmanuel et al., 2002). Therefore, the concentration of 10 μM used here to investigate the effects of prucalopride on action potentials, refractoriness, and arrhythmic activity was 1000-fold higher than its normal therapeutic concentration in humans. Nevertheless, despite using atrial cells from patients with prior treatment with β-adrenoceptor antagonists, which has been shown to increase the incidence of 5-HT-induced arrhythmic contrac-

**Fig. 7.** Effect of prucalopride and 5-HT on arrhythmic activity in human atrial myocytes. Effect of 5-HT, but not of prucalopride, to promote abnormal depolarizations in a human atrial myocyte and its blockade by the specific 5-HT₄ antagonist GR-113808. An example of original recordings of action potentials obtained from a single human atrial myocyte (paced at 75 bpm), before (A), in the presence of 10 μM prucalopride (B), 10 μM 5-HT (C) (following 3-min washout of prucalopride), and then blockade of 5-HT-induced abnormal depolarizations by 1 μM GR-113808 (D).

Hence, our finding of lower potency remains relevant to patients who have not been receiving β-adrenoceptor antagonists.

To date, nine 5-HT₄ receptor subtypes (5-HT₄a–i/hb/n) have been identified and localized in the human body (Langlois and Fischmeister, 2003; Brattelid et al., 2004), but only some of these (5-HT₄a–c, 5-HT₄g, 5-HT₄i, and 5-HT₄n) have been shown to be present in the human atrium (Bach et al., 2001; Medhurst et al., 2001; Vilaro et al., 2002; Brattelid et al., 2004). In addition, the pharmacological properties of the 5-HT₄ isoforms have been associated with different receptor levels of expression (Bach et al., 2001; Medhurst et al., 2001;
tions (Sanders et al., 1995) and abnormal depolarizations (Pau et al., 2003), we have shown that 10 μM prucalopride did not induce abnormal depolarizations in any of the atrial cells studied. In contrast, 10 μM 5-HT, after perfusion with 10 μM prucalopride, induced abnormal depolarizations in ~27% of the cells studied, which is also consistent with our previous observations in human atrial myocytes (Pau et al., 2003). It is noteworthy that in the study by Sanders et al. (1995), the partial 5-HT4 agonist, renzapride, was not reported to produce arrhythmic contractions in human atrial cells, whereas 5-HT produced such contractions in human atrial cells and strips. In the present study, it is evident that prucalopride lacked arrhythmogenic activity because it acts as a partial rather than a full agonist and caused a significantly smaller increase in ICaL and calcium loading than did 5-HT.

There is major concern about the potential for ventricular arrhythmias when using 5-HT4 receptor agonists as gastrokinetic agents (Tonini et al., 1999; Yusuf et al., 2003). This is related to the ability of several drugs, including the enterokinetic agent, to block IKr, with associated prolongation of the repolarization phase of the ventricular action potential that underlies the acquired long QT syndrome (Viskin, 1999). The only report of effects of prucalopride on IKr encoded by cardiac HERG demonstrated that at micromolar concentrations, prucalopride significantly blocked HERG current expressed in a kidney cell line (Potet et al., 2001). However, at therapeutic concentrations, prucalopride had no effect on the QT interval in humans (De Schryver et al., 2002; Krogh et al., 2002), consistent with a lack of effect of prucalopride on human ventricular IKr. The present findings in human atrial myocytes of a lack of effect of prucalopride on late repolarization and refractoriness are also consistent with an absence of effect on atrial delayed rectifier K+ current. An additional mechanism by which prucalopride might affect action potential duration would be by influencing the time course of inactivation of ICaL, as well as its peak density, but we demonstrated here that prucalopride and 5-HT had no effects on ICaL inactivation in human atrial cells.

In conclusion, these data indicate that, in the human atrium, the prucalopride-induced increase in calcium current was associated with prolongation of the early phase of action potential repolarization but not late repolarization, refractoriness, or arrhythmic activity. Moreover, prucalopride, when compared with 5-HT, behaved as a partial rather than full agonist in enhancing ICaL and APD90 in human atrial myocytes. These results further support the hypothesis that the expression of specific 5-HT4 receptor subtypes in human atrial cells may mediate different functional electrophysiological responses to different agonists, and this needs to be taken into account when using 5-HT4 agonists in humans.

Acknowledgments

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