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# Dopamine receptor agonists differ in their actions on cardiac ion channels

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**Abstract**

Four dopamine receptor agonists used for the treatment of Parkinson's disease (apomorphine, pergolide, ropinirole and sumanirole) were evaluated for the ability to block human ether-a-go-go related gene (hERG) $K^+$ channels and to modify the duration of canine Purkinje fiber action potentials. Apomorphine, pergolide and ropinirole blocked the hERG-mediated currents with $IC_{50}$ values of 2.4, 0.12 and 1.2 μM, respectively. When evaluated in an action potential duration assay, pergolide significantly shortened action potential duration at 90% repolarization ($APD_{90}$) whereas apomorphine and ropinirole significantly prolonged repolarization. Sumanirole only partially blocked hERG $K^+$ channels at the highest tested concentration (10 μM) and did not modify action potential duration over the tested concentration range (0.65–65 μM). Taken together, these data provide evidence that dopamine receptor agonists developed for the treatment of Parkinson's disease differentially influence hERG $K^+$ channel function and cardiac action potential duration.


*Keywords:* Parkinson's disease; Dopamine receptor agonist; hERG channel; Action potential duration

## 1. Introduction

Prolongation of the QT interval of the electrocardiographic waveform is an established risk factor for the development of the potentially life threatening ventricular arrhythmia torsades de pointes (for review, see Redfern et al., 2003). Retrospective studies have shown that most drugs associated with QT interval prolongation and/or torsades de pointes also block human ether-a-go-go related gene (hERG) $K^+$ channels, which underlie the cardiac repolarizing $K^+$ current $I_{Kr}$ (Curran et al., 1995; Sanguinetti et al., 1995). However, not all drugs that block hERG necessarily increase the risk of torsades de pointes (Yang et al., 2001). For example, verapamil is a relatively potent hERG channel blocker but is not associated with increased risk of torsades de pointes (Bril et al., 1996; Chouabe et al., 1998).

Idiopathic Parkinson's disease is characterized by the presence of α-synuclein-rich Lewy bodies and neuronal loss within specific regions of the nervous system (for reviews, see, Braak and Braak, 2000; Sherer et al., 2001). In addition to the hallmark impairment of motor function, Parkinson's disease is associated with disturbances of both the sympathetic and parasympathetic branches of the autonomic nervous system (Chaudhuri, 2001; Piha et al., 1988; Ørskov et al., 1987; Awerbuch and Sandyk, 1994). As a result, patients with Parkinson's disease have an increased risk of impaired cardiovascular function (Szili-Török et al., 2001; Kallio et al., 2000; Mathias, 1998). As with other disorders of autonomic function, recent studies suggest that Parkinson's disease may be associated with a prolongation of the QT interval, and it has been suggested that the degree of prolongation is related to disease severity (Bexton et al., 1986; Browne et al., 1982; Ahnve and Vallin, 1982; Choy et al., 1998; Oka et al., 1997; Quadri et al., 2000). Drugs with the potential to prolong the QT interval may impose an added risk to individuals with Parkinson's disease (Mathias, 1998). Therefore, the present study was undertaken to evaluate the potential for antiparkinsonian drugs to influence the QT

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interval as determined by two in vitro assays that are commonly used to assess cardiac ion channel function. Four dopamine receptor agonists developed for the treatment of Parkinson's disease were evaluated. Apomorphine, pergolide, ropinirole and sumanirole were each tested for the ability to block hERG $K^+$ channels and/or to modify canine Purkinje fiber action potential duration.

## 2. Materials and methods

### 2.1. Cell culture

Chinese hamster ovary (CHO-K1) cells stably expressing hERG channels were obtained from GENION (Hamburg, Germany). Cells were grown in Minimum Essential Medium (MEM) alpha supplemented with 10% heat inactivated fetal bovine serum, penicillin (100 U/ml) + streptomycin (100 μg/ml) and geneticin (G418, 800 μg/ml). Cells were maintained in a humidified incubator at 37 °C and 6% $CO_2$. Electrophysiological recordings were conducted 1–2 days after plating cells onto uncoated or poly-L-lysine coated glass cover slips. Cells plated on cover slips were grown without geneticin.

### 2.2. Purkinje fiber tissue preparation

Purpose bred male mongrel hounds of at least 1 year of age were euthanized with an overdose of methohexital (Jones Pharma, St. Louis, MO). The heart was quickly excised and placed in ice cold, oxygenated (95%$O_2$/5%$CO_2$) modified Tyrode's solution at a pH of 7.25–7.4 of the following composition (in mM): NaCl 132, KCl 3, $MgCl_2$ 1.5, $CaCl_2$ 2.0, $KH_2PO_4$ 1.25, glucose 5.55 and $NaHCO_3$ 16. Sections from the base of the left ventricle which had a well developed Purkinje fiber network were dissected out and excess tissue was trimmed away leaving the resulting tissue section about 2–3 mm thick. The tissue section was pinned down to a silastic surface on the bottom of a glass, water-jacketed tissue superfusion chamber. Warmed (35–37 °C), oxygenated modified Tyrode's solution flowed over the tissue at a rate of 12–15 ml/min. A bipolar stimulating electrode was aligned to touch the surface of the tissue section and stimulating pulses of 2 ms were generated using a Master 8 stimulator (A.M.P.I., Jerusalem, Israel) to evoke action potentials.

### 2.3. Voltage-clamp electrophysiology

Currents were recorded from CHO-K1 cells using the whole-cell patch clamp technique with an Axopatch 200B amplifier (Axon Instruments, Union City, CA). hERG-mediated currents were evoked using an action potential (AP) voltage-clamp protocol; AP commands were applied once per second from a holding potential of −80 mV. The AP used in this protocol was obtained from a canine Purkinje fiber paced at 1 Hz. Signals were acquired at 200 μs/point and filtered at 1000 Hz. Whole-cell currents were digitized, stored, and measured using pCLAMP software (Axon Instruments). Cells expressing from 400 to 2000 pA of peak hERG-mediated current were included in this study. Cells were continuously superfused with an external bath solution containing (in mM): NaCl 109, $NaHCO_3$ 26, KCl 4.2, $CaCl_2$ 2, $MgCl_2$ 1.5, $NaH_2PO_4$ 1.2, HEPES 20, glucose 10, L-glutamine 2; L-ascorbic acid 0.28 (pH to 7.4 with NaOH, ~300 mosM). L-glutamine and L-ascrobic acid, which are components of the growth medium, were observed to minimize the extent of current run-down in initial experiments; these reagents did not otherwise modify the hERG-mediated currents when tested at the same concentration (data not shown). Patch pipettes were pulled from borosilicate capillary glass using a Flaming/Brown

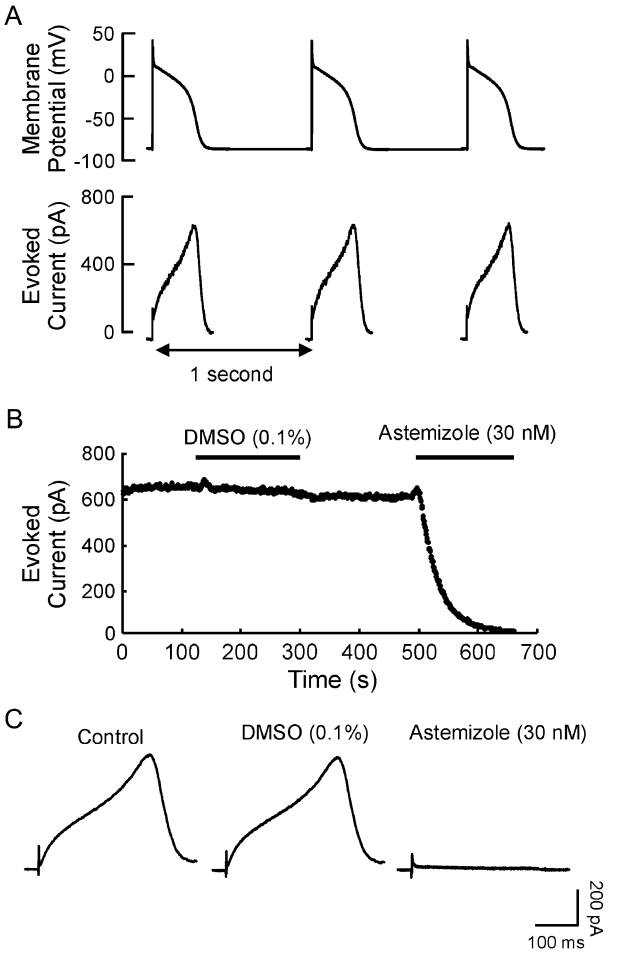


Fig. 1. Action potential voltage-clamp protocol. (A) Upper panel: voltage clamp command that was used in this study. The action potential was measured from a canine Purkinje fiber paced at 1 Hz. Pulses were applied once per second from a holding potential of −80 mV. Lower panel: Example of hERG-mediated currents that were evoked using the action potential voltage-clamp protocol. (B) Example of a control experiment showing the effect of DMSO (0.1%) and astemizole (30 nM) on the peak hERG-mediated current; horizontal bars indicate the time of exposure to the test compound. (C) Example current traces recorded during the experiment shown in (B).

micropipette puller (P97, Sutter Instrument, Novato, CA) and filled with an internal pipette solution consisting of (in mM): K-methanesulfonate 125, KCl 10, $MgCl_2$ 1, EGTA 5, HEPES 10, ATP-Mg 3, GTP-Na 0.3, phosphocreatine 4 (pH 7.2, ~ 290 mosM). The resistances of the patch pipettes when filled with internal pipette solution ranged from 3 to 6 MΩ. Experiments were conducted at 34–36 °C. Test solutions were added for 3 min or until a new steady-state amplitude was obtained. Peak currents determined from the average of 30 consecutive sweeps recorded during the baseline period were compared to the peak current from the average of 30 consecutive sweeps recorded in the presence of a test solution. Current blockade was plotted in percent according to Blockade (%) = $100*(1 - (I_{test}/I_{baseline}))$ where $I_{test}$ is the current measured in the presence of the test solution and $I_{baseline}$ is the current measured prior to exposure to the test solution; each cell served as its own control. $IC_{50}$ values were determined according to Blockade (%) = $100*([compound]^n/[compound]^{n+} IC_{50}^n))$ where $n$, the Hill slope, was constrained to unity.

### 2.4. Current-clamp electrophysiology

Action potentials were recorded from Purkinje fibers with an Axoclamp 2B amplifier (Axon Instruments). Glass microelectrodes were pulled on a Flaming/Brown P-97 electrode

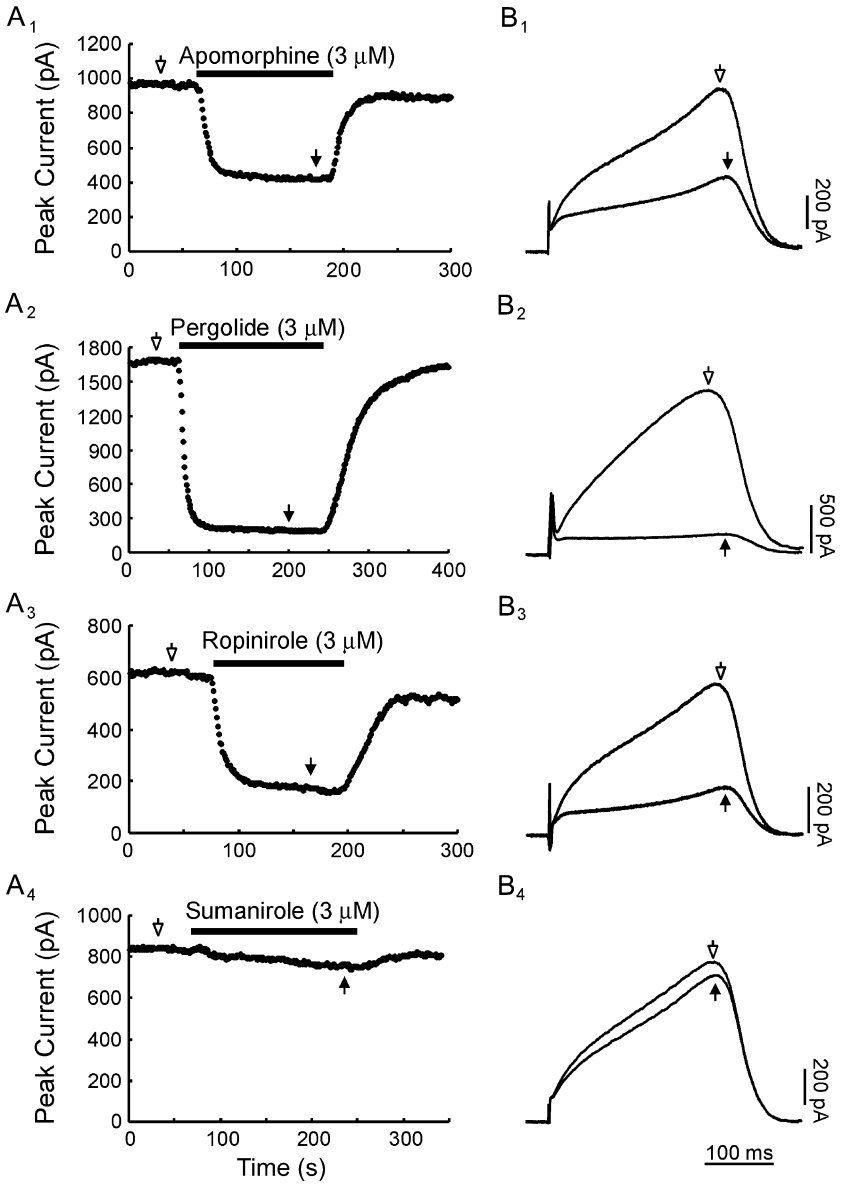


Fig. 2. Blockade of hERG-mediated current by dopamine receptor agonists. Examples of blockade produced by 3 μM of each compound. (A) Plots show the peak amplitude as a function of time for apomorphine ($A_1$), pergolide ($A_2$), ropinirole ($A_3$) and sumanirole ($A_4$). After establishing a stable baseline response, test compounds were applied for the time indicated by the horizontal bar. (B) Examples of the currents evoked during the baseline line period (open arrow) and the test period (filled arrow) for apomorphine ($B_1$), pergolide ($B_2$), ropinirole ($B_3$) and sumanirole ($B_4$). Traces shown are the average of 30 consecutive sweeps.

puller (Sutter Instrument) and filled with 3M KCl. The tissue sections were allowed to equilibrate for 60–90 min before initiating experiments. Modified Tyrode's solution was used as the external solution for recording action potentials. Tissue sections were exposed to test compounds while stimulating at 1 Hz for a period of 15–25 min at each concentration. Each compound was tested on six different tissue sections; each tissue section originated from a different animal. Recordings were obtained from either one or two Purkinje fibers per tissue section. When measurements were obtained from two fibers, the data were averaged and treated as single value in subsequent analysis. Parallel time-matched vehicle control experiments were conducted for each compound using a separate tissue section from the same animals. Action potentials were recorded and subsequently analyzed for the duration at 90% repolarization using pCLAMP software. For each tissue section, the mean baseline $APD_{90}$ value was subtracted from the test value to calculate the change in $APD_{90}$. The baseline-adjusted data were analyzed by a repeated measures analysis of variance (Gill, 1978). Comparisons were made between the vehicle and drug groups at each time point with Tukey's honest significant difference method (Milliken and Johnson, 1984). Resulting *P*-values are two-sided, and comparisons with $P < 0.05$ were considered statistically significant. All statistical analyses were performed with the GLM Procedure in the SAS® System For Windows™ Version 6.12. Data are presented as mean ± S.E.M.

### 2.5. Materials

Cell culture reagents were purchased from Life Technologies (Rockville, MD). Astemizole and cisapride were purchased from Research Diagnostics (Flanders, NJ). Apomorphine and pergolide were purchased from Sigma (St. Louis, MO). Ropinirole hydrochloride was obtained by extraction from pharmaceutical tablets of Requip®. The extracted ropinirole hydrochloride was further purified by flash chromatography eluting with methanol in methylene chloride and then crystallized from acetonitrile. The crystallized material had a melting point of 233–246 °C and all analytical data was consistent for the product. Sumanirole was obtained from the Medicinal Chemistry Department, Pharmacia (Kalamazoo, MI). Stock solutions of apomorphine, pergolide and sumanirole were prepared in dimethyl sulfoxide (DMSO); stock solutions of ropinirole were prepared in water. Stock solutions were prepared fresh daily and diluted into the bath solution containing a final concentration of 0.1% DMSO.

## 3. Results

### 3.1. Effects of dopamine receptor agonists of hERG $K^+$ channels

The dopamine receptor agonists apomorphine, ropinirole, pergolide and sumanirole were each evaluated for the ability to block hERG $K^+$ channels stably expressed in CHO-K1 cells. hERG-mediated currents were evoked using a cardiac action potential voltage clamp protocol while maintaining the cells under physiologically relevant conditions (Fig. 1A). As illustrated in Fig. 1B and C, the evoked currents were stable and not significantly modified by the vehicle in subsequent experiments (0.1% DMSO, inhibition = 2.3 ± 1.1%, $n = 7$), but were blocked greater than 90% by 30 nM astemizole, a known potent hERG $K^+$ channel blocker (inhibition = 93.4 ± 5.3%, $n = 11$; for reference, see Zhou et al., 1999).

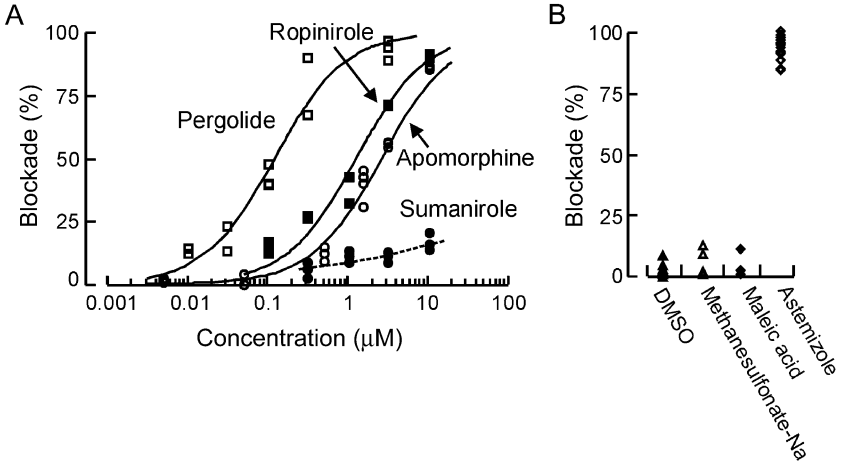


Fig. 3. Concentration–response relationships for blockade of hERG-mediated currents. (A) Symbols are the block determined from individual cells for apomorphine (open circles, $n = 20$), pergolide (open squares, $n = 13$), ropinirole (filled squares, $n = 12$) and sumanirole (filled circles, $n = 12$). The solid lines through the data points for apomorphine, pergolide and ropinirole were obtained by fitting a logistic function with Hill slope of one to the data; the dashed line through the data for sumanirole was drawn by eye. (B) Values of blockade for the control compounds are plotted against the same *y*-axis as the test compounds. Data points indicate the results from individual cells for 0.1% DMSO ($n = 7$), 1.5 μM methanesulfonate–Na ($n = 4$), 10 μM maleic acid ($n = 3$) and 30 nM astemizole ($n = 11$).

Bath application of the highest tested concentration of apomorphine (10 μM), pergolide (3 μM), ropinirole (10 μM) and sumanirole (10 μM) blocked the peak evoked hERG-mediated current by 86.0 ± 0.5% ($n = 3$), 92.9 ± 2.2% ($n = 3$), 90.4 ± 0.5% ($n = 3$) and 16.5 ± 2.0% ($n = 3$), respectively. Pergolide was not tested at 10 μM due to the limited aqueous solubility of this compound. As illustrated in Fig. 2, the blockade produced by each drug occurred rapidly and was readily reversed upon washout, and none of the drugs produced a notable change in the kinetics of the response. The concentration–response for apomorphine, ropinirole and pergolide were each well-described by a simple logistic function with an $IC_{50}$ value of 2.4, 1.2 and 0.12 μM, respectively (continuous curves in Fig. 3A). No $IC_{50}$ value could be determined for sumanirole due to the low-level of blockade observed over the tested concentration range.

Whereas apomorphine and ropinirole were prepared as a hydrochloride salt, pergolide was prepared as a mesylate salt and sumanirole was prepared as a salt of maleic acid. Due to the possibility that these small organic counterions contributed to the inhibition produced by pergolide and sumanirole, sodium methanesulfonate and maleic acid were tested for the ability to inhibit hERG-mediated currents. As illustrated in Fig. 3B, sodium methanesulfonate (1.5 μM) reduced the peak current by 5.4 ± 2.8% ($n = 4$) and maleic acid (10 μM) reduced the peak current by 4.2 ± 3.1% ($n = 3$). These

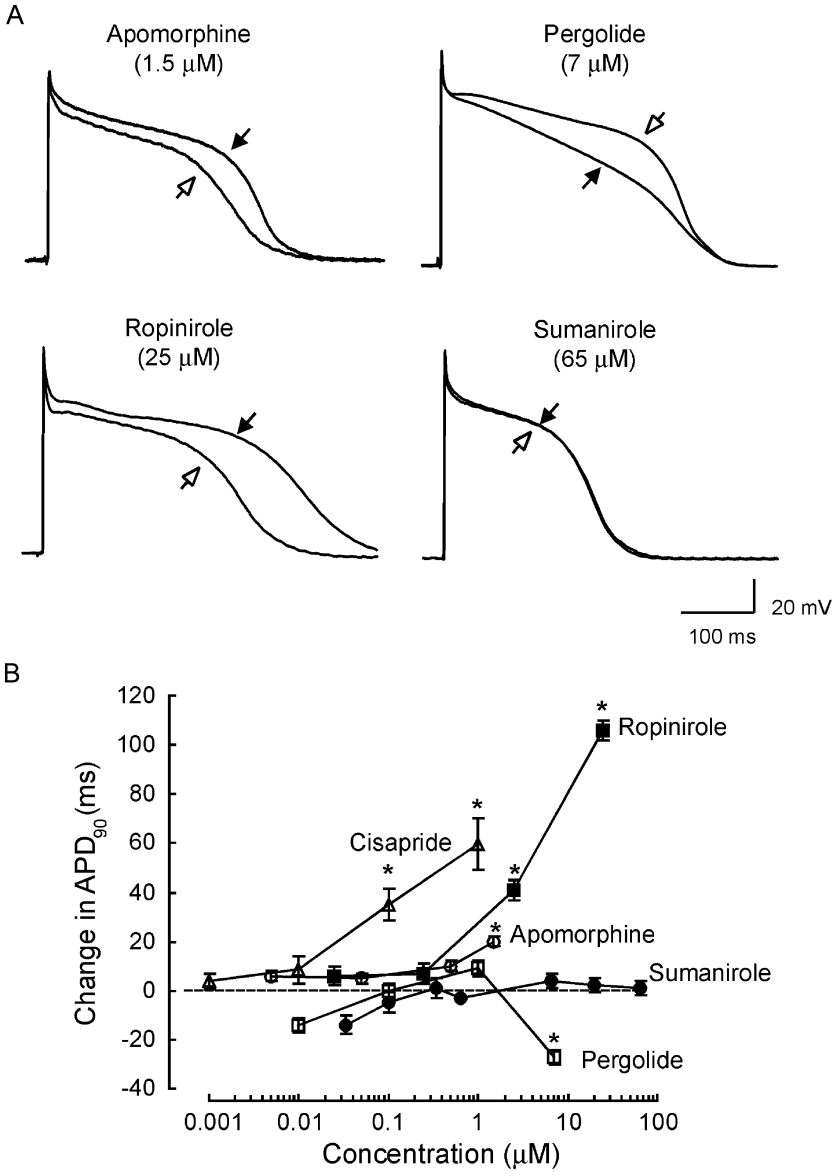


Fig. 4. Effects of dopamine receptor agonists on action potential duration. (A) Examples of action potentials evoked during the baseline period (open arrow) and during exposure to the indicated concentration of apomorphine, ropinirole, pergolide and sumanirole (filled arrow). (B) Concentration–response relationships of the effects on $APD_{90}$ of apomorphine (open circles), pergolide (open squares), ropinirole (filled squares), sumanirole (filled circles). For comparison, the concentration–response for cisapride is shown on the same plot (open triangles). Data points marked with an asterisk were significantly different from the time-matched vehicle control ($P < 0.05$).

values are not different from the level of blockade produced by 0.1% DMSO suggesting that the counterions did not significantly block hERG channels at these concentrations.

### 3.2. Effects of dopamine receptor agonists on action potential duration

Numerous studies have shown that most drugs that block hERG $K^+$ channels can also prolong the cardiac action potential and/or increase the QT interval (for review, see Redfern et al., 2003). Therefore, apomorphine, pergolide, ropinirole and sumanirole were evaluated for the ability to modulate the duration of action potentials recorded from canine Purkinje fibers. Action potentials were evoked before and during exposure to a series of concentrations of each drug. For statistical evaluation, change in $APD_{90}$ produced by each test compound was compared to the change observed in time-matched vehicle control experiments. Examples of evoked action potentials measured before and during drug exposure and the concentration–response relationships are shown in Fig. 4. Consistent with the observed blockade of hERG, apomorphine prolonged $APD_{90}$ by $20 \pm 2$ ms ($n = 6$, $P < 0.05$) at 1.5 μM, and ropinirole prolonged $APD_{90}$ by $41 \pm 4$ ms ($n = 6$, $P < 0.05$) and $106 \pm 4$ ms ($n = 6$, $P < 0.05$) at 2.5 and 25 μM, respectively. For comparison, the effects of cisapride, which is known to prolong the QT interval in humans, is also shown (Rampe et al., 1997; Mohammad et al., 1997; van Haarst et al., 1998). Sumanirole produced no statistically significant effect on action potential duration over the tested concentration range (0.65–65 μM), which is consistent with its low-level of hERG blockade. While pergolide tended to prolong at 1 μM ($9 \pm 4$ ms, $n = 6$, not significant), the highest tested concentration (7 μM) significantly shortened $APD_{90}$ by $27 \pm 3$ ms ($n = 6$, $P < 0.05$).

## 4. Discussion

The present study evaluated four drugs developed for the treatment of Parkinson's disease in two preclinical models that are commonly used to assess cardiovascular safety. Sumanirole produced minimal blockade of the hERG-mediated current at concentrations up to 10 μM and the effect was only weakly concentration-dependent (Fig. 3). Consistent with this observation, sumanirole produced no detectable change in action potential duration over this concentration range and up to 65 μM. Apomorphine, ropinirole and pergolide each produced a concentration-dependent blockade of the hERG-mediated current that was well described by simple logistic function with a Hill slope of one. Pergolide was the most potent hERG blocker with an $IC_{50}$ of approximately 120 nM; however, pergolide produced only a slight trend toward prolongation at 1 μM ($9 \pm 4$ ms, not significant) but shortened action potential duration at the highest concentration of 7 μM. These findings are similar to previous results showing that low concentrations of verapamil prolong whereas higher concentrations shorten cardiac action potential duration (Cranefield et al., 1974; Kass and Tsien, 1975; Zhang et al., 1997). The shortening of action potential duration, which could have been produced either by pergolide or the mesylate counterion, is presumed to result from effects on ion channels other than hERG. Of the other three compounds tested, a relatively good relationship was observed between hERG blockade and prolongation of $APD_{90}$. The rank order potency in both assays was ropinirole>apomorphine≫sumanirole. While the effects of sumanirole were small in both assays, the concentrations of ropinirole and apomorphine interpolated to produce a 20-ms prolongation of $APD_{90}$ (0.6 and 1.5 μM, respectively) were both associated with about a 30% inhibition of hERG-mediated current ($IC_{30} = 0.5$ and 1.1 μM, respectively).

In summary, these results suggest that apomorphine, ropinirole, pergolide and sumanirole interact with cardiac ion channels and modulate cardiac action potential duration to different extents. Pergolide was the most potent blocker of the hERG $K^+$ channel and may block additional cardiac ion channels based on its effects on the Purkinje fiber action potential. Apomorphine and ropinirole blocked hERG channels and prolonged action potential duration over similar concentrations suggesting that these drug interact primarily with the hERG $K^+$ channel. In contrast, sumanirole had a minimal effect on hERG $K^+$ channels and did not modify action potential duration over the tested concentration range.

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