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Risperidone reduces K^+ currents in human atrial myocytes and prolongs repolarization in human myocardium

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Abstract

The antipsychotic agent risperidone has been shown to cause QT prolongation. In rabbit heart preparations, we have demonstrated that risperidone markedly lengthened action potential duration and blocked the delayed rectifier current, $I_{Kr.}$ The current study was designed to investigate the risperidone effects: (i) on the main K^+ repolarizing currents on human atrial myocytes, using whole-cell patch clamp recordings; (ii) on action potentials recorded from human atrial and ventricular myocardium using conventional microelectrodes. We found that: (1) risperidone (3–30 μM) reduced significantly the sustained current, I_{sus}, and 30 μM decreased significantly the transient outward current I_{to} but was without effect on the inward rectifier current I_{K1}; (2) risperidone (0.3–10 μM) lengthened significantly the final repolarization of the atrial action potential and risperidone (10 μM) markedly lengthened the final repolarization in ventricular myocardium. This study showed that risperidone exerts direct electrophysiological effects on human preparations but only at relatively high concentration.

Keywords: Risperidone; Heart, human; Outward potassium current; Action potential

1. Introduction

Risperidone is an antipsychotic agent commonly used in the treatment of schizophrenia and other psychoses. Risperidone exerts antagonistic effects on 5-hydroxytryptamine (5-HT_2), dopamine (D2), α_1- and α_2-adrenoceptors and histamine (H_1) receptors. In contrast with other antipsychotics such as haloperidol and chlorpromazine, it allows a clear improvement of the quality of life of the patients by a reduction in specific extrapyramidal effects.

Similarly to a great number of antipsychotics (Cavero et al., 2000; Haverkamp et al., 2000), risperidone has been implicated in several cases of QT interval lengthening, the majority of them occurring with risperidone overdosage (Brown et al., 1993; Lo Vecchio et al., 1996; Laroussinie et al., 1997; Kopala et al., 1998). However, to our knowledge, no case of torsades de pointes was reported with risperidone.

In most of cases, QT prolongation by non-cardiac drugs involved a reduction of repolarizing K^+ currents, particularly the rapid component of the delayed rectifier current I_{Kr}. At cellular level, this results in a prolongation of the cardiac action potential duration (for review, see Haverkamp et al., 2000). In a previous study (Gluais et al., 2002), we showed that 0.3 μM risperidone reduced by about 50% the I_{Kr} current recorded in rabbit ventricular myocytes and that 0.1 μM risperidone lengthened significantly the action potential duration recorded both in rabbit Purkinje fiber and ventricular myocardium. At low stimulation frequency (0.2 Hz), we observed the development of early after-depolarizations in the presence of 3 μM risperidone in

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Purkinje fiber and 10 μM risperidone in ventricular myocardium. It has been shown that 3 μM risperidone prolonged the action potential duration at 90% repolarization recorded in ventricular guinea-pig myocardium by about 27% (Botchway et al., 2002) and 10 μM risperidone prolonged the final action potential repolarization by about 20% in guinea-pig papillary muscle and by about 10% in isolated cardiac canine myocyte, concurrently with a reduction of I_{Kr} current (Magyar et al., 2002). These results provide evidence that in several animal species risperidone possesses a proarrhythmic potentiality. Nevertheless, it is evident that the greatest care must be taken in extrapolating these results to humans.

Recent studies realized on the *Human-Ether-a-gogo-Related-Gene* (HERG) cloned channel, which expresses the K^+ channel that underlies I_{Kr} in human heart (Sanguinetti et al., 1995) showed that risperidone was able to block this channel with an IC_{50} value of 1.6 μM (Frederiksen and Adamantidis, 2000), 0.394 μM (Lacerda et al., 2001) and 0.148 μM (Ekins et al., 2002).

In human atrium, the transient outward K^+ current (I_{to}), the sustained current (I_{sus}), the inwardly rectifying K^+ current (I_{K1}) represent the major outward currents and thus play an important role in the shape and duration of the human atrial action potential. I_{Kr} and I_{Ks} have also been described in human atrial myocytes (Wang et al., 1994) but not in all myocytes and with only relatively small densities in comparison with the densities of I_{to} and I_{sus} currents. For these reasons, only I_{to}, I_{sus} and I_{K1} were examined in our study. The aim of the present study was to investigate: (i) the effects of risperidone on the voltage-dependent ionic currents, I_{to}, I_{sus} and I_{K1} recorded from isolated human atrial myocytes; (ii) the electrophysiologic effects of risperidone on action potentials recorded from human atrial and ventricular myocardium.

2. Materials and methods

Specimens of human right atrial appendage and left ventricular myocardium were obtained from patients undergoing open-heart surgery (atrial appendage) or mitral valve replacement (ventricular myocardium). Patient details are shown in Table 1. The study was approved by the Ethical Committee of the institution (Centre Hospitalier et Universitaire de Lille). Samples were immersed in a cardioplegic solution containing (in mM): NaCl 147, KCl 20, $MgCl_2$ 16, $CaCl_2$ 0.5, $NaHCO_3$ 25, glucose 55, pH 7.4, warmed at 30 °C gassed by carbogen (95% O_2–5% CO_2) and transported quickly to the laboratory.

Table 1
Clinical characteristics of the patients

Study	Sex	Diagnosis	Age	Previous medication
PC	F	CI	75	ramipril, atenolol, acarbose, pravastatine
	M	CI	78	sotalol, amlodipine, nicorandil
	M	CI	70	sotalol
	F	CI	68	trinitrine, acebutolol, aspirin, molsidomine, omeprazole
	M	CI	67	aspirin, lithium, molsidomine, propranolol
	M	AI	74	none
	M	AI	61	propranolol, molsidomine, aspirin, omeprazole
A-AP	F	CI	75	ramipril, atenolol, acarbose, pravastatine
	F	CI	56	atenolol, atorvastatine, molsidomine, aspirin
	M	CI	71	atenolol, pravastatine
V-AP	F	MI	80	ramipril, furosemide, digoxin, potassium chloride, acarbose
	F	MI	78	ramipril, digoxin, furosemide, heparine

PC: patch-clamp, risperidone; A-AP: atrial action potential; V-AP: ventricular action potential; CI: coronary insufficiency; AI: aortic insufficiency; MI: mitral insufficiency.

2.1. Atrial and ventricular myocyte preparation

2.1.1. Myocyte isolation

Myocytes were enzymatically isolated as follows: small pieces of atrial tissue were cut up and washed in calcium-free Krebs-Ringer solution containing (in mM): NaCl 35, KCl 4.75, KH_2PO_4 1.19, $NaHPO_4$ 16, HEPES 10, glucose 10, $NaHCO_3$ 25, saccharose 134 and 2,3-butanedione oxime 30, pH 7.4, gassed with carbogen and maintained at 37 °C. Pieces were reincubated in the same solution without 2,3-butanedione oxime and containing bovine serum albumin (5 mg/ml, DADE-Behring, La Defense, France), 200 IU/ml collagenase (type IV Sigma, Saint Quentin Fallavier, France) and 6 IU/ml protease (type XXIV, Sigma). After 30 min of digestion, the small pieces were incubated in an enzyme solution containing only collagenase (400 IU/ml) for twice 10 min. Then, the supernatant was filtered and completed with an HEPES/bovine serum albumin solution containing bovine serum albumin (bovine serum albumin, 20 mg/ml, Biomedical Technologies, Stoughton, MA, USA) and (in mM) HEPES 25, NaCl 130, glucose 5, KCl 4.8, KH_2PO_4 1.2, pH 7.4, gassed with oxygen. It was centrifuged at 1000 rpm for 1 min and the pellet was resuspended in the same solution. After three complete digestions, the bovine serum albumin/HEPES cell solutions were added (v/v) with a storage solution of Dulbecco's Mode Eagle Medium (Life Technologies, Invitrogen, Cergy Pontoise, France) supplemented with non-essential amino acids (Life Technologies), antibiotics (penicillin 100 UI/ml, streptomycin 0.1 mg/ml) (Sigma) and fetal bovine serum (10%, Life Technologies). The cell suspension was centrifuged at 1000 rpm for 1 min and the pellet was resuspended in 3 ml storage solution. The cell preparation was stored at room temperature and used between 2 and 8 h after isolation.

2.1.2. Current measurements

Currents were recorded by using the patch-clamp technique in the whole-cell configuration. Currents were recorded using a RK 400 amplifier (Bio-Logic, Claix, France) and pClamp software (Axon Instrument, Foster City, CA, USA). The voltage clamp protocol was a series of (i) 750-ms voltage steps from −50 to +60 mV (10-mV increments) from a holding potential of −80 mV for I_{to} and I_{sus}; (ii) 240-ms voltage steps from −140 to +10 mV (10-mV increment) from a holding potential of −40 mV, for I_{K1}. The amplitude of the rapidly inactivating current (I_{to}) was measured as the difference between the peak of the outward K^+ current and the current measured at the end of 750-ms test pulses. The amplitude of the sustained current (I_{sus}) was measured as the difference between the amplitude of the current measured at the end of the 750-ms test pulses and the zero current. The steady-state current amplitude of I_{K1} was measured as the end of each voltage pulse. Currents were sampled at 3.33 and 6.25 kHz, respectively, for I_{to}, I_{sus} and I_{K1} using a 12-bit analog-to-digital converter (Labmaster TL-1, Scientific Solutions, Solon, OH, USA), low-pass filtered at 3 kHz. Borosilicate glass pipettes (Clark Electromedical Instruments, Reading, UK) had a resistance of 1.7–2 MΩ when filled with the pipette solution (in mM: KCl 130, $MgCl_2$ 2, HEPES 10, K_2ATP 3, phosphocreatine 5, EGTA 10), pH 7.2. The external solution used had the following composition (in mM): NaCl 54, *N*-methyl-D-glucamine 86, KCl 4, $MgCl_2$ 1, HEPES 10, $CaCl_2$ 1, glucose 10, tetrodotoxin 0.02, $CoCl_2$ 3, pH 7.4. Control and drug-containing solutions were applied to the exterior of the cell by placing it at the opening of 300 μm inner diameter catheters fixed on the rotating head of a rapid solution changer (RSC, Bio-Logic). Cell capacitance was measured by integrating the area of the capacitive transient elicited by 5 mV hyperpolarizing steps. The atrial cells capacitance was 99.4±9.5 pF (n=16). Currents were normalized to the membrane capacity to eliminate variation of the cell size. Data were analysed using pClamp (Axon Instrument). All experiments were carried out at room temperature (20–22 °C).

2.2. Multicellular preparations

Small pieces of atrial or ventricular tissues were carefully pinned, endocardium upward, to the silicone base of the experimental chamber. The preparations were superfused with a normal Tyrode's solution (in mM: NaCl 118.2, KCl 4, $CaCl_2$ 1.8, $MgCl_2$ 1, NaH_2PO_4 1.8, $NaHCO_3$ 25, glucose 11) pH 7.4±0.05, at a flow rate of 2.5 ml/min, gassed with carbogen (95% O_2–5% CO_2) and thermostated at 36.0±0.5 °C. The atrial preparations were stimulated at the frequency of 2 Hz and the ventricular preparations at the frequency of 0.5 Hz by rectangular pulses of 1-ms duration, with an intensity 1.5 times higher than the diastolic threshold of stimulation. Pulses were delivered by a stimulator (SCE 20, Electronique Appliquée, Montrouge, France) through a bipolar Teflon-insulated (except at the tip) stainless-steel electrode. After 30 min, the two types of preparations were stimulated at the frequency of 1 Hz and allowed to equilibrate during at least 90 min.

2.2.1. Action potential recordings

Transmembrane action potentials were recorded using conventional glass microelectrodes filled with 3 M KCl and having tip resistance of 10–20 MΩ, coupled with an Ag–AgCl bath electrode and connected to an impedance amplifier (VF 102 Bio-Logic). Action potentials were viewed on an oscilloscope (Gould DSO 1602, Cleveland, OH, USA), analyzed by an external computer system (Datapac, Bio-Logic) and stored on a magnetic digital tape recorder (DTR 1205, Bio-Logic), which, after each experiment, allowed to display on paper recordings (Gould TA 240, Cleveland, OH, USA) the action potential and electrical abnormalities (e.g. early afterdepolarization). The following parameters of action potential were measured: resting membrane potential, action potential amplitude, maximal rate of depolarization (V_{max}) and action potential duration at 50% and 90% of repolarization.

2.2.2. Experimental protocol: concentration-dependent effects

After at least 90-min stabilization and before application of risperidone, the stimulation frequency was reduced from 1 to 0.2 Hz for 2 min, then returned to 1 Hz. This maneuver was performed only for ventricular myocardium and aimed to examine the influence of a low rate of stimulation on action potential characteristics and to verify the absence of abnormality in repolarization, such as early afterdepolarization. Then, increasing concentrations (0.03, 0.1, 0.3, 1, 3 and 10 μM) of risperidone were applied in a cumulative manner, each concentration being applied during 30 min. The frequency of stimulation was 1 Hz except during 2 min (between the 20th and the 22nd minute) where the frequency was lowered to 0.2 Hz then switched back to 1 Hz. Action potential parameters were measured at the end of the 30-min perfusion of each concentration and at the end of each period of 2-min stimulation at 0.2 Hz. Only the results obtained when the impalement was maintained in the same cell throughout the experiment have been considered for quantitative evaluation.

2.3. Drugs

Stock solution (10 mM) of risperidone (Sigma) was prepared extemporarily and later diluted in the external solution (when recording currents) or in Tyrode's solution (when recording the action potential) to the desired concentration. Risperidone powder was dissolved as follows: 4.1 mg were dissolved in 1 ml of dimethylsulfoxide. The influence of the vehicle was tested in a previous study and was found without significant effect. Tetrodotoxin (Latoxan, Valence, France) was prepared as a 1 mM stock

solution in citrate buffer solution. All other chemicals were obtained from Sigma.

2.4. Statistical evaluation

All results are presented as mean±standard error of the mean and *n* indicates the number of observations. Comparisons among groups were performed by using an analysis of variance (ANOVA) for repeated measures and corrected by Dunnett's *t*-test or by Student's *t*-test for two groups. Differences with $P<0.05$ were considered statistically significant.

3. Results

3.1. Risperidone and K^+ currents

3.1.1. Concentration-dependent inhibitory effects of risperidone on I_{to} and I_{sus}

In human atrial myocytes, the voltage-activated outward K^+ currents is essentially composed of two components: an initial rapidly inactivating component, the transient outward current I_{to}, followed by a slowly inactivating sustained component I_{sus} which itself consists of two currents, a potassium current carried by Kv1.5 referred to as the ultrarapid delayed rectifier current (I_{Kur}) and the non-selective cation current I_{ns} (Crumb et al., 1995). Fig. 1A gives representative traces of currents elicited by 10-mV incremental 750-ms test pulses from a holding potential of −80 mV recorded in the same cell in control and after 5 min of external application of 0.3 and 3 μM risperidone. Fig. 1B shows the density–voltage relationships of I_{to} in control and after 5 min of risperidone (0.03–30 μM) exposure. Risperidone reduced dose-dependently I_{to} current density but this effect reached the significant level only at the highest concentration of 30 μM at potentials above 10 mV. A total of 30 μM risperidone reduced the maximum current density of I_{to} measured at 60 mV from 11.52±0.93 to 8.17±0.45 pA/pF (n=7, $P<0.05$). The averaged current density–voltage relationships of I_{sus} obtained in control and after (0.03–30 μM) risperidone are shown in Fig. 1C. Risperidone decreased in dose-dependent manner the current density of I_{sus} and this effect was already significant at the concentration of 3 μM from +10 mV to more positive potentials, 4.41±0.50 to 3.14±0.31 pA/pF at +60 mV (n=9) and at 30 μM from 4.75±0.55 to 2.50±0.25 pA/pF at +60 mV (n=7).

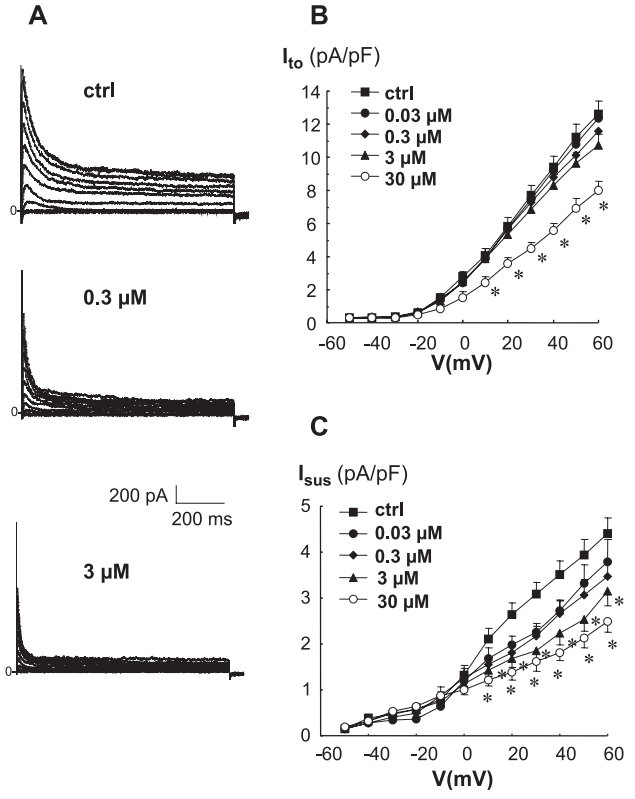

Fig. 1. Concentration-dependent effects of risperidone on I_{to} and I_{sus} recorded in human atrial myocytes. (A) Example of currents traces are shown in control and after 5-min superfusion of 0.3 and 3 μM risperidone. Averaged current density–voltage relations of I_{to} (B) and I_{sus} (C), in control and after exposure to 0.03–30 μM risperidone (n=5 for 0.03 and 0.3 μM, n=7 for 3 μM and n=6 for 30 μM risperidone). *$P<0.05$ vs. control (ctrl). Risperidone 30 μM reduced significantly the current density of I_{to} from +10 mV to more positive potentials. Risperidone 3 and 30 μM reduced the current density of I_{sus} from +10 mV to more positive potentials.

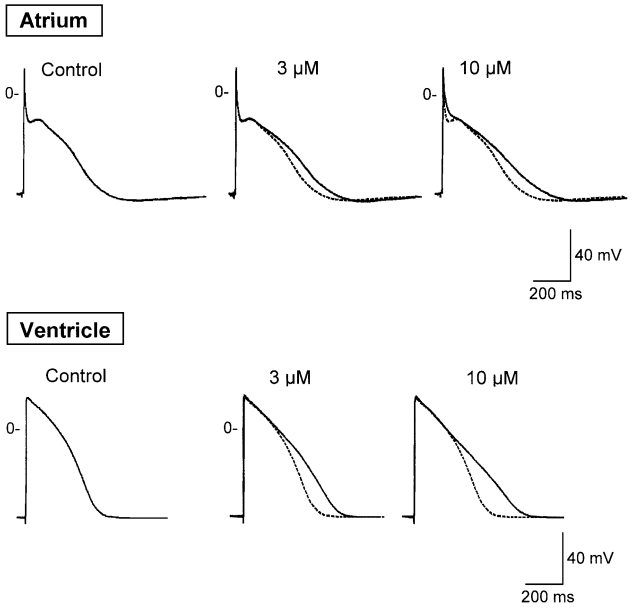

Fig. 2. Representative example of the prolonging effects exerted by risperidone on repolarization in action potentials recorded from human atrial and ventricular myocardium stimulated at 1 Hz. Control drug-free action potentials are superimposed in dotted line.

3.1.2. Risperidone effects on the inward rectifier current I_{K1} recorded in human atrial myocytes

Two cumulative concentrations of risperidone (3 and 30 μM) were tested on I_{K1} and each concentration being maintained for 5 min. A total of 3 μM risperidone was

Table 2
Concentration dependent effects induced by risperidone on action potential parameters recorded in atrial myocardium stimulated at the frequency of 1 Hz

	Control	Risperidone (μM)			
		0.3	1	3	10
RMP (mV)	−76±1	−76±3	−79±1	−78±1	−79±2
APA (mV)	100±5	97±7	100±7	100±7	93±6
V_{max} (V/s)	228±35	206±37	187±31	189±36	134±28[a]
APD_{50} (ms)	152±4	160±12	174±15	171±13	170±16
APD_{90} (ms)	333±17	367±18[a]	400±18[a]	430±17[a]	451±23[a]

RMP: resting membrane potential; APA: action potential amplitude; V_{max}: maximal rate of depolarization; APD_{50} and APD_{90}: action potential duration at 50% and 90% repolarization, respectively (n=5).
[a] P<0.05 vs. control values.

without effect on I_{K1}, whereas the highest concentration of risperidone (30 μM) reduced slightly the steady-state current density in the potential range of −120 to −100 mV but this effect did not reach the significant level (data not shown).

3.2. Risperidone and action potential

3.2.1. Risperidone effects on action potential recorded from human atrial myocardium

A representative example of risperidone effects (3–10 μM) on the action potential in human atrial myocardium is illustrated in Fig. 2 (top). The action potential recorded in control showed a large spike-and-dome aspect and a relatively steep phase 3 repolarization. Risperidone at concentrations above 0.3 μM induced a concentration-dependent lengthening in action potential duration particularly at final repolarization level. At the highest concentration tested (10 μM), the spike was widened and the dome disappeared and the lengthening affected only the final repolarization. Table 2 summarizes the effects obtained on the action potential parameters, recorded in five experiments. The lengthening effect on the final repolarization (i.e. action potential duration at 90% of repolarization) was already significant (vs. control values) at the concentration of 0.3 μM (367±18 vs. 333±17 ms), 10 μM risperidone reduced significantly the V_{max} but resting membrane potential, action potential amplitude and action potential duration at 50% of repolarization remained unaltered.

3.2.2. Risperidone effects on action potential recorded from human ventricular myocardium

These experiments were carried out on ventricular myocardium obtained from two patients. Fig. 2 (bottom) illustrates the effects of increasing concentrations (3–10 μM) of risperidone on the action potential recorded in ventricular myocardium. Risperidone concentration-dependently lengthened the action potential duration. This effect was particularly marked on the final repolarization at the concentration of 10 μM risperidone. Table 3 summarizes the effects obtained on action potential parameters. The low number of preparations prevented us to realize any statistical analysis. However, the final repolarization (i.e. action potential duration at 90% of repolarization) was strongly prolonged with increasing concentrations of risperidone (0.03–10 μM), 484±25 ms at 10 μM vs. 370±19 ms in control, this lengthening effect was slightly enhanced by lowering the stimulation rate from 1 to 0.2 Hz, 521±35 ms at 10 μM vs. 400±27 ms in control. On the other hand, risperidone was without effect on the other action potential parameters, resting membrane potential, action potential amplitude and V_{max}.

4. Discussion

The results presented in this study provide evidence that risperidone exerts direct cardiac electrophysiological effects in human myocardium. Actually, 3 μM risperidone reduced significantly the current density of I_{sus} and 30 μM the current density of I_{to} both recorded in atrial myocytes. Furthermore, risperidone (0.3–10 μM) prolonged the action potential duration recorded in atrial and ventricular myocardium.

4.1. I_{to}/I_{sus} and atrial action potential

I_{sus} was more sensitive to risperidone blocking effects than I_{to} since it was significantly reduced by 3 μM risperidone and

Table 3
Concentration-dependent effects induced by risperidone on action potential parameters recorded in human ventricular myocardium stimulated at the frequency of 1 Hz

	Control	Risperidone (μM)					
	(n=4)	0.03 (n=2)	0.1 (n=2)	0.3 (n=2)	1 (n=2)	3 (n=4)	10 (n=4)
RMP (mV)	−83±1	−82±1	−80±3	−85±1	−83±1	−82±0	−82±0
APA (mV)	113±2	110±2	109±4	112±2	113±1	113±1	113±1
V_{max} (V/s)	229±26	247±13	241±23	244±77	267±74	267±74	204±44
APD_{50} (ms)	262±14	272±16	276±12	279±11	295±7	292±14	294±13
APD_{90} (ms)							
(a)	369±19	386±19	390±13	399±12	425±9	440±24	484±25
(b)	400±27	416±23	432±23	440±12	473±15	481±35	521±35

RMP: resting membrane potential; APA: action potential amplitude; V_{max}: maximal rate of depolarization; APD_{50} and APD_{90}: action potential duration at 50% and 90% repolarization, respectively. n=number of preparations. (a) stimulation frequency of 1 Hz, (b) stimulation frequency of 0.2 Hz.

I_{to} by 30 μM. Both concentrations 3 and 30 μM risperidone are 10 and 100 times higher than the experimental concentration of 0.3 μM risperidone considered as clinically relevant (Gluais et al., 2002). However, a recent study demonstrates that risperidone concentration was 4.5-fold higher in cardiac tissue than in plasma (Titier et al., 2002) so that the experimental concentrations which affected I_{sus} and I_{to} could occur, particularly in cases of overdosage.

Recent advances in molecular biology have resulted in the cloning of a variety of genes that may underlie voltage-dependent K^+ channels. Among these channels, Kv4.3 underlies the transient outward current I_{to} (Kaab et al., 1998; Wang et al., 1999) in human atrial and ventricular myocardium, and Kv1.5 is thought to underlie the ultrarapid activating delayed rectifier current I_{Kur}, which is the major component of I_{sus} (Fedida et al., 1993; Wang et al., 1993). Our results are in agreement with a recent study that evidenced the inhibition of Kv4.3 and Kv1.5 by risperidone (Lacerda et al., 2001). Actually, these authors showed that risperidone blocked Kv4.3 channel with an IC_{50} of 25.5 μM and Kv1.5 channel with an IC_{50} of 9.5 μM and in the present study, 30 μM risperidone inhibited I_{to} by 30% and I_{sus} by about 50%. The blocking effect on I_{sus} induced by low concentration of risperidone and to a lesser degree the reduction of I_{to} at highest concentration may play a determinant role in the lengthening effect on the atrial action potential, which was dose-dependently prolonged by increasing concentrations of risperidone. Similar results are reported with flecainide and quinidine, which prolong the atrial action potential to the same extent (Wang et al., 1990) but through the decrease in I_{to} by flecainide and decrease in both I_{to} and I_{sus} by quinidine (Wang et al., 1995). Furthermore, using a mathematical model, Nygren et al. (1998) found that action potential at 90% of repolarization was prolonged by 27% with a widened spike and an elevated action potential plateau, when I_{to} and I_{sus} are both reduced by 40%. Interestingly, similar modifications were seen on the action potential in the presence of 10 μM risperidone. On the other hand, risperidone was without effect on the inward rectifier current I_{K1}, in accordance with the fact that resting membrane potential and action potential amplitude were not modified.

In a previous study, we have demonstrated that 30 μM risperidone reduced significantly I_{to} current in rabbit atrium without affecting the sustained current (Gluais et al., 2002). The different effects observed on the sustained current between rabbit and human can be likely related to the differences in the ionic nature of I_{sus}. Actually, I_{sus} in rabbit atrium is believed to be carried by Cl^- ions (Lindblad et al., 1996), whereas I_{sus} in human atrium is carried mainly by K^+ ions (Firek and Giles, 1995; Brandt et al., 2000).

4.2. Ventricular action potential and risperidone

In ventricular preparations, risperidone prolonged the action potential duration, particularly at final repolarization level represented by the duration of action potential at 90% of repolarization. This effect attained +15% at the concentration of 1 μM and +31% at 10 μM.

Among the side effects that can be associated with noncardiac drugs, prolongation of cardiac repolarization may be responsible for the development of polymorphic ventricular tachycardia, the so-called torsades de pointes, particularly if predisposing factors such as congenital long QT syndrome, bradycardia, hypokalemia and/or hypomagnesemia are present (for review, see Volders et al., 2000). To our knowledge, no case of torsades de pointes was reported with risperidone. This proarrhythmic activity is characterized by a prolongation of the QT interval on the electrocardiogram consequently to a reduction of the repolarizing current in particular the rapid component of the delayed rectifier current I_{Kr}. Some cases of QT prolongation (especially during risperidone overdosage) have been reported in literature (Brown et al., 1993; Lo Vecchio et al., 1996; Laroussinie et al., 1997; Kopala et al., 1998). In the great majority of cases, the non-cardiac drugs known to prolong the ventricular repolarization are potent blockers of the *Human-Ether-a-gogo-Related-Gene* (HERG) channel which expresses the K^+ channel that underlies I_{Kr} in human heart (Sanguinetti et al., 1995). In this respect, risperidone blocking effect on HERG was studied by different researchers, who found an IC_{50} of 1.6 μM (Frederiksen and Adamantidis, 2000), 0.394 μM (Lacerda et al., 2001) and 0.148 μM (Ekins et al., 2002). Although the same mammalian cell lines were used to express the HERG channel in the three studies, the differences between IC_{50} for HERG inhibition suggest some influence likely due to different experimental procedures (Ekins et al., 2002). The concentrations which blocked 50% of HERG channel seemed to be low compared to the concentration which increased the ventricular action potential duration. This highlights the necessity to combine the different electrophysiological approaches (HERG, native currents, action potential recordings) for evaluating the proarrhythmic potentiality of a drug.

On the other hand, risperidone effects on the cardiac repolarization have been studied in several animal species. Thus, we reported recently in rabbit ventricular myocardium that risperidone prolonged potently the action potential duration since 1 and 10 μM lengthened the duration of action potential at 90% of repolarization by 47% and 147%, respectively (Gluais et al., 2002), whereas guinea-pig and dog ventricular myocardium were found less sensitive to risperidone effects (Botchway et al., 2002; Magyar et al., 2002). These interspecies differences in action potential risperidone effect could be explained by the variations in the types, kinetics and amplitudes of the outward currents, specially I_{to} and I_{Kr}. Furthermore, we have demonstrated that 0.3 μM risperidone reduced by about 50% the I_{Kr} current in rabbit ventricular myocytes and that 30 μM risperidone reduced significantly the I_{K1} current recorded in

rabbit ventricular myocytes whereas in canine ventricular myocyte, risperidone blocked the I_{Kr} current with an IC_{50} of 0.92 μM and was without effect on I_{to} and I_{K1} currents (Magyar et al., 2002).

5. Conclusion

The studies performed in human cell preparations involve inherently uncontrolled differences in patient drug treatment, gender, disease state and small numbers of preparations. However, the present results demonstrated that in humans risperidone prolonged the atrial action potential partly by reducing I_{sus} and I_{to} currents and the ventricular action potential at concentrations reported to block the HERG current and could occur in cases of overdosage. Despite this arrhythmogenic potentiality, there is only one case of death following cardiac arrest after administration of a therapeutic dose of risperidone in absence of cardiovascular antecedent (Ravin and Levenson, 1997). In agreement with a recent review on the potential cardiac risk of antipsychotics (Glassman and Bigger, 2001) and as discussed in our previous paper (Gluais et al., 2002), several factors other than cardiac direct electrophysiological effects bradycardia, electrolyte disorders, drugs interactions, female gender and associates pathologies should be taken into consideration for evaluating the potential for serious cardiac adverse events. In conclusion, risperidone presents a moderate risk to cause ventricular arrhythmia if no predisposing factors are associated.

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