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The effect of α_2-adrenoceptor antagonists in isolated globally ischemic rat hearts

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Abstract

The α_2-adrenoceptor antagonist, yohimbine, has been reported to protect hypoxic myocardium. Yohimbine has several other activities, including 5-HT receptor antagonism, at the concentrations at which protection was found. Therefore we designed a study to determine if yohimbine was protecting ischemic myocardium via antagonism of α_2-adrenoceptors. In isolated globally ischemic rat hearts, the effects of two structurally distinct classes of α_2-adrenoceptor antagonists, the indole alkaloids (yohimbine and rauwolscine) and the imidazolines (idozoxan and tolazoline) were investigated. Pretreatment with yohimbine (1–10 μM) caused a concentration-dependent increase in reperfusion left ventricular developed pressure and a reduction in end diastolic pressure and lactate dehydrogenase release. The structurally similar compound rauwolscine (10 μM) also protected the ischemic myocardium. In contrast, idozoxan (0.3–10 μM) or tolazoline (10 μM) had no protective effects. The cardioprotective effects of yohimbine were partially reversed by 30 μM 5-HT. These results indicate that the mechanism for the cardioprotective activity of yohimbine may involve 5-HT receptor antagonistic activity.

Key words: α_2-adrenoceptor antagonist; 5-HT (5-hydroxytryptamine, serotonin); Myocardial ischemia

1. Introduction

The physiological role of α-adrenoceptors in the cardiovascular system has been studied by a number of investigators. Stimulation of post-synaptic α_1-adrenoceptors modulates the release of Ca^{2+} via either a phosphatidylinositol-dependent or -independent pathway (Van Zwieten, 1989). The physiological response to stimulation of α_2-adrenoceptors depends on the localization of the receptors. The overall response is due to stimulation of central α_2-adrenoceptors which causes vasodilation and a corresponding decrease in blood pressure. However, stimulation of peripheral pre-synaptic and post-synaptic α_2-adrenoceptors can inhibit norepinephrine release and causes vasoconstriction and an increase in blood pressure. Antagonists of pre-synaptic α_2-adrenoceptors increase norepinephrine release which in turn stimulates post-synaptic adrenoceptors (Reichenbacher et al., 1982). Antagonism of central α_2-adrenoceptors increases blood pressure and heart rate in conscious animals and man (Goldberg and Robertson, 1983; Rockhold and Gross, 1981; Van Zwieten, 1989).

Following myocardial ischemia an increase in norepinephrine overflow has been documented (Dart et al., 1984; Schomig et al., 1984). Furthermore norepinephrine is thought to induce cardiotoxicity at concentrations equivalent to those produced during myocardial ischemia (Dart et al., 1984; Rona, 1985; Schomig et al., 1984). The norepinephrine overflow documented is not due to central adrenoceptors, but peripheral exocytotic release (Dart et al., 1984). Several investigators have shown that selective and non-selective α_1-adrenoceptor antagonists can protect ischemic myocardium (Nayler et al., 1985; Sharma et al., 1983; Takeo et al., 1988; Tanonaka et al., 1989). A recent study has demonstrated that in the isolated hypoxic rat heart, the α_2-adrenoceptor antagonist yohimbine improves cardiac function and metabolism (Takeo et al., 1991).

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These results suggested that stimulation of norepinephrine release via antagonism of peripheral α_2-adrenoceptors, may actually be an endogenous protective mechanism for the ischemic myocardium. However, the concentrations of yohimbine required to improve hypoxic cardiac function and metabolism are higher than those required to stimulate norepinephrine release (Takeo et al., 1991). Therefore, a secondary activity of yohimbine may be responsible for the observed cardioprotection. Yohimbine has several other activities including serotonin antagonism, α_1-adrenoceptor antagonism, dopamine antagonism, monoamine oxidase inhibition and local anesthetic activity (Goldberg and Robertson, 1983). Yohimbine can act as a 5-HT receptor antagonist at concentrations similar to those shown to be cardioprotective (Lambert et al., 1978; Shaw and Woolley, 1953). Our laboratory has recently reported that 5-HT_2 receptor antagonists protect globally ischemic rat hearts (Grover et al., 1993). Therefore, we determined if the cardioprotective effects of yohimbine were due to α_2- or 5-HT receptor antagonism utilizing two structurally distinct classes of α_2-adrenoceptor antagonists, the indole alkaloids (yohimbine and rauwolscine) and the imidazolines (idozoxan and tolazoline).

2. Materials and methods

2.1. Isolated rat hearts

2.1.1. Preparation of the isolated hearts

Male Sprague-Dawley rats (400–450 g) were anesthetized using 100 mg/kg sodium pentobarbital (i.p.). They were intubated and then treated with i.v. heparin (1000 U/kg). While being mechanically ventilated, their hearts were perfused in situ via retrograde cannulation of the aorta. The hearts were then excised and quickly moved to a Langendorff apparatus, where they were perfused with Krebs-Henseleit solution containing (in mM): 112 NaCl, 25 $NaHCO_3$, 5 KCl, 1.2 $MgSO_4$, 1 KH_2PO_4, 1.25 $CaCl_2$, 11.5 glucose and 2 pyruvate at a constant perfusion pressure (85 mm Hg). A water-filled latex balloon attached to a metal cannula was then inserted into the left ventricle and connected to a Statham pressure transducer for measurement of left ventricular pressure. The hearts were allowed to equilibrate for 15 min, at which time end diastolic pressure (EDP) was adjusted to 5 mm Hg and this balloon volume was maintained for the duration of the experiment. Pre-ischemic or pre-drug function, heart rate and coronary flow (extracorporeal electromagnetic flow probe, Carolina Medical Electronics, King, NC) were then measured. Left ventricular developed pressure (LVDP) was calculated from the difference between left ventricular peak systolic pressure and EDP. Cardiac temperature was maintained throughout the experiment by submerging the hearts in 37°C buffer which was allowed to accumulate in a stoppered, heated chamber.

2.2. Experimental protocol

2.2.1. Effect of α_2-adrenoceptor antagonists in globally ischemic rat hearts

The hearts were divided into groups as follows. (1) Hearts treated with vehicle (0.04% dimethylsulfoxide, DMSO; $n = 8$) 2. Hearts treated with 0.3–10 μM yohimbine ($n = 4$ per group) 3. Hearts treated with 10 μM rauwolscine ($n = 4$) 4. Hearts treated with 0.3–10 μM idozoxan ($n = 4$ per group) 5. Hearts treated with 10 μM tolazoline ($n = 4$). All drugs were given in the perfusate for 10 min prior to the onset of ischemia. Global ischemia was initiated by completely shutting off the perfusate flow, and this global ischemia was maintained for 25 min. Reperfusion with Krebs-Henseleit solution without any of the drugs was then initiated, and the hearts were allowed to recover for 30 min. Reperfusion, cardiac function and coronary flow were then measured. The reperfusion effluent was sampled for cumulative lactate dehydrogenase (LDH) release. LDH was determined using a kit supplied by Boehringer Mannheim based on the technique of Wroblewski and LaDue (1955). LDH release was expressed as U/g pre-ischemic heart weight for the 30-min collection period. LDH release was used as an indicator of cellular viability or membrane integrity (Van der Laarse et al., 1979).

2.2.2. Effect of 5-HT receptor and the α_2-adrenoceptor agonist clonidine on the cardioprotective effects of yohimbine

In a separate series of experiments hearts were divided into groups as follows. (1) Hearts treated with vehicle (0.04% DMSO $n = 8$). (2) Hearts treated with 1 and 10 μM yohimbine ($n = 8$ per group). (3) Hearts treated with 100 μM clonidine ($n = 4$). This concentration of clonidine has been previously reported to stimulate tissue α_2-adrenoceptors (Frankhuyzen and Mulder, 1982). (4) Hearts treated with 100 μM clonidine + 1 μM yohimbine. (5) Hearts treated with 30 μM 5-HT ($n = 4$); (6) Hearts treated with 30 μM 5-HT + 10 μM yohimbine ($n = 4$). All drugs were given in the perfusate for 10 min prior to the onset of ischemia. An identical experimental protocol as described above was then conducted.

2.3. Statistics

All values are expressed as mean ± S.E.M. Changes in contractile function and LDH levels were analyzed using an ANOVA followed by an unpaired t-test. Significance was accepted if $P \leq 0.05$.

3. Results

The effect of the α_2-adrenoceptor antagonists yohimbine and rauwolscine on pre- and post-ischemic cardiac function is shown in Table 1. After treatment with 10 μM yohimbine or rauwolscine, a significant reduction in LVDP from vehicle values was observed prior to ischemia. A significant reduction in coronary flow and heart rate from vehicle was also observed after treatment with 10 μM yohimbine. During global ischemia both yohimbine and rauwolscine increased time to contracture compared to vehicle-treated hearts. These data are not shown as time to contracture was greater than 25 min (the total period of ischemia) in many of the groups. After 30 min reperfusion, no changes in heart rate were observed after treatment with either yohimbine or rauwolscine. LVDP was significantly increased after treatment with 1 and 10 μM yohimbine and 10 μM rauwolscine. Significant reductions in reperfusion EDP and LDH release were also observed after treatment with 1 μM and 10 μM yohimbine and 10 μM rauwolscine (Fig. 1), further indicating that these compounds protect ischemic myocardium.

Pretreatment with the imidazolines, idozoxan (0.3–10 μM) and tolazoline (10 μM) did not significantly alter pre-ischemic heart rate, LVDP or coronary flow (Table 2). No significant effects were observed in ischemic time to contracture or post-ischemic heart rate, LVDP, EDP or LDH release after treatment with either idozoxan or tolazoline (Table 2, LDH and time to contracture data not shown). There were significant increases in coronary flow upon reperfusion with idozoxan, but this was not a dose-dependent phenomenon. There was also a significant increase in reperfusion coronary flow after treatment with 10 μM tolazoline.

Pretreatment with the α_2-adrenoceptor agonist clonidine (100 μM) resulted in a significant reduction in pre-ischemic heart rate (Table 3). Pre-ischemic LVDP was significantly increased in the presence of 100 μM clonidine. Post-ischemic heart rate was unaltered after pretreatment with 100 μM clonidine whereas significant reductions were observed in LVDP and coronary flow relative to vehicle. No changes in reperfusion LDH were found after clonidine pretreatment versus vehicle (Fig. 2). A significant increase in reperfusion EDP was seen after clonidine treatment (Fig. 2). In the presence of 100 μM clonidine none of the pre-ischemic effects of yohimbine were changed. Even though clonidine was slightly pro-ischemic yohimbine still caused a significant increase in reperfusion LVDP and reduction in EDP and LDH release in the presence of clonidine.

Pretreatment with 30 μM 5-HT had no significant effect on pre-ischemic heart rate (Table 4). A significant reduction was observed in pre-ischemic coronary flow and LVDP after 30 μM 5-HT pretreatment. Post-ischemic heart rate, LVDP, coronary flow, EDP and LDH release were unaltered in the presence of 30 μM 5-HT when compared to vehicle (Table 4; Fig. 3). Pre-ischemic coronary flow was significantly reduced in the presence of 5-HT or yohimbine yet, unexpectedly co-treatment resulted in no significant changes in pre-ischemic coronary flow (Table 4). The significant re-

Table 1
Effect of yohimbine and rauwolscine on cardiac function and coronary flow

	Pre-ischemia		30 min post reperfusion
	Pre-drug	Post-drug	
HR (beats / min)			
Vehicle	268 ± 8	262 ± 11	268 ± 8
Yohimbine 0.3 μM	269 ± 9	249 ± 2	256 ± 7
Yohimbine 1 μM	280 ± 5	258 ± 5 [a]	268 ± 4
Yohimbine 10 μM	283 ± 4	74 ± 6 [a,b]	264 ± 3 [a]
Rauwolscine 10 μM	294 ± 11	250 ± 11 [a]	289 ± 16
LVDP (mm Hg)			
Vehicle	138 ± 5	129 ± 5	30 ± 3 [a]
Yohimbine 0.3 μM	147 ± 3	135 ± 6	28 ± 2 [a]
Yohimbine 1 μM	131 ± 5	114 ± 7	79 ± 2 [a,b]
Yohimbine 10 μM	136 ± 6	104 ± 5 [a,b]	101 ± 3 [a,b]
Rauwolscine 10 μM	125 ± 6	105 ± 5 [a,b]	83 ± 7 [a,b]
Coronary flow (ml / min per g)			
Vehicle	17.2 ± 1.8	16.7 ± 1.6	12.7 ± 1.0 [a]
Yohimbine 0.3 μM	19.5 ± 2.0	15.5 ± 1.0	15.1 ± 1.7
Yohimbine 1 μM	19.1 ± 1.0	16.8 ± 1.2	15.5 ± 1.1
Rauwolscine 10 μM	20.1 ± 0.8	21.9 ± 0.9 [b]	17.6 ± 1.9 [b]

All values are means ± S.E.M., HR = heart rate, LVDP = left ventricular developed pressure. [a] Significantly different from its respective pre-drug value ($P < 0.05$). [b] Significantly different from its respective vehicle group value ($P < 0.05$).

Table 2
Effect of idazoxan and tolazoline on cardiac function and coronary flow

	Pre-ischemia		30 min post reperfusion
	Pre-drug	Post-drug	
HR (beats / min)			
Vehicle	287 ± 13	293 ± 11	254 ± 17
Idozoxan 0.3 μM	270 ± 13	256 ± 10	260 ± 46
Idozoxan 1 μM	270 ± 6	259 ± 2	249 ± 26
Idozoxan 3 μM	288 ± 7	272 ± 4	275 ± 7
Idozoxan 10 μM	285 ± 6	253 ± 7	247 ± 31
Tolazoline 10 μM	282 ± 18	273 ± 16	234 ± 37
LVDP (mm Hg)			
Vehicle	140 ± 8	130 ± 5	38 ± 7 [a]
Idozoxan 0.3 μM	133 ± 2	132 ± 3	30 ± 7 [a]
Idozoxan 1 μM	141 ± 2	137 ± 3	34 ± 4 [a]
Idozoxan 3 μM	135 ± 6	131 ± 5	22 ± 8 [a]
Idozoxan 10 μM	141 ± 4	139 ± 6	34 ± 9 [a]
Tolazoline 10 μM	138 ± 9	126 ± 10	34 ± 9 [a]
Coronary flow (ml / min per g)			
Vehicle	17.1 ± 1.2	16.6 ± 0.7	11.6 ± 0.8 [a]
Idozoxan 0.3 μM	19.0 ± 2.0	16.3 ± 1.8	12.8 ± 1.5 [a]
Idozoxan 1 μM	20.0 ± 1.2	17.0 ± 0.6	14.5 ± 0.7 [a,b]
Idozoxan 3 μM	21.4 ± 2.4	17.7 ± 3.0	14.6 ± 1.5
Idozoxan 10 μM	19.5 ± 1.8	16.9 ± 2.0	14.4 ± 1.1
Tolazoline 10 μM	20.4 ± 1.6	19.1 ± 1.9	15.1 ± 1.0 [a,b]

All values are means ± S.E.M., HR = heart rate, LVDP = left ventricular developed pressure. [a] Significantly different from its respective pre-drug value ($P < 0.05$). [b] Significantly different from its respective vehicle group value ($P < 0.05$).

ductions in pre-ischemic LVDP observed after treatment with yohimbine were still observed after co-treatment with 5-HT (Table 4). In the presence of 5-HT, the improvement in reperfusion LVDP observed after pretreatment with yohimbine was partially reversed. No significant changes from vehicle were seen in either reperfusion heart rate or coronary flow after co-treatment with yohimbine and 5-HT. Following reperfusion, 30 μM 5-HT abolished the effect of yohimbine on EDP and reduced the effect of yohimbine on LDH (Fig. 3). Measurement of reperfusion EDP and LDH demonstrated that the significant reduction in these

Table 3
Effect of clonidine in the absence or presence of yohimbine on cardiac function and coronary flow

	Pre-ischemia		30 min post reperfusion
	Pre-drug	Post-drug	
HR (beats / min)			
Vehicle	285 ± 6	281 ± 8	235 ± 17 [a]
100 μM clonidine	291 ± 7	184 ± 17 [a,b]	250 ± 43
1 μM yohimbine	280 ± 5	257 ± 5	268 ± 4
1 μM yohimbine + clon	242 ± 13 [b]	156 ± 21 [a,b]	237 ± 20
LVDP (mm Hg)			
Vehicle	134 ± 2	125 ± 3	23 ± 4 [a]
100 μM clonidine	132 ± 3	157 ± 2 [a,b]	5 ± 1 [a,b]
1 μM yohimbine	131 ± 5	114 ± 7	79 ± 2 [a,b]
1 μM yohimbine + clon	142 ± 5	174 ± 6 [a,b]	81 ± 14 [a,b]
Coronary flow (ml / min per g)			
Vehicle	21.4 ± 1.1	21.1 ± 1.1	15.0 ± 0.9 [a]
100 μM clonidine	17.2 ± 1.2 [b]	15.8 ± 1.3 [b]	8.8 ± 0.6 [a,b]
1 μM yohimbine	19.1 ± 1.0	16.8 ± 1.2 [b]	1.5 ± 1.6
1 μM yohimbine + clon	18.7 ± 0.5	17.7 ± 0.8	16.3 ± 0.8

All values are means ± S.E.M., HR = heart rate, LVDP = left ventricular developed pressure. [a] Significantly different from its respective pre-drug value ($P < 0.05$). [b] Significantly different from its respective vehicle group value ($P < 0.05$).

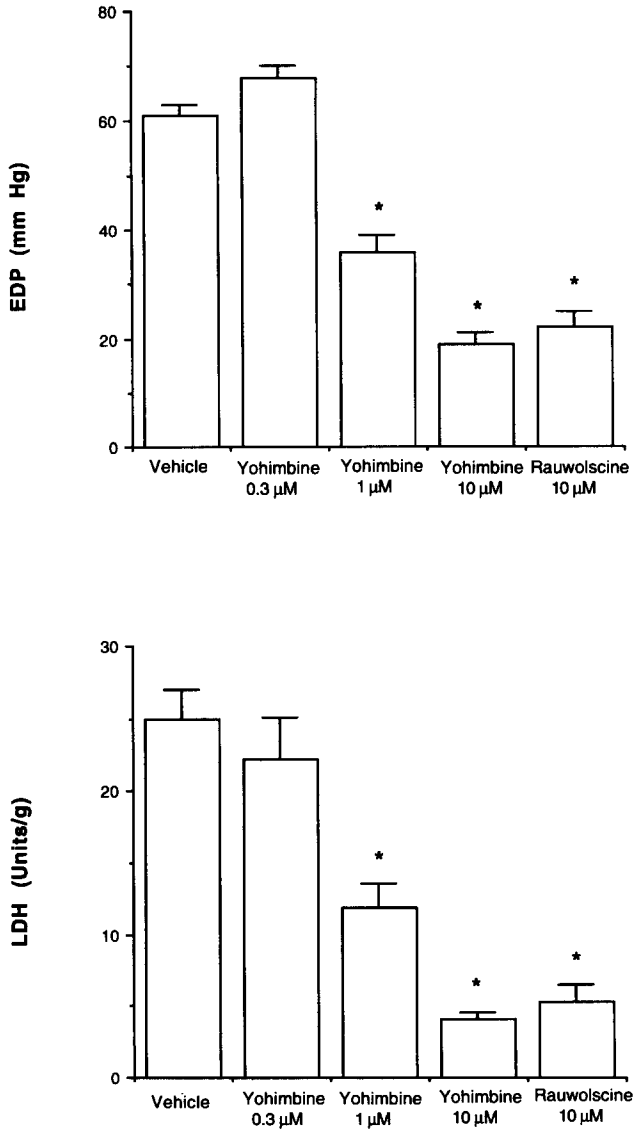

Fig. 1. The effect of yohimbine or rauwolscine on EDP and cumulative LDH release at 30 min into reperfusion following 25 min global ischemia in isolated rat hearts. Yohimbine (1 and 10 μM) and rauwolscine (10 μM) significantly reduced both EDP and LDH release (* $P > 0.05$).

parameters by yohimbine was abolished in the presence of 30 μM 5-HT.

4. Discussion

In this study, we demonstrated that protection of the ischemic myocardium is not an activity common to all compounds which antagonize α_2-adrenoceptors. The imidazoline antagonists did not protect the ischemic myocardium even though they have been demonstrated to be specific for α_2-adrenoceptors (Daibre, 1986; Galitzky et al., 1989). There are several reports which demonstrate that idozoxan binds to two sites in many tissues (Michel et al., 1989; Tibirica et al., 1991). One site is common to all α_2-adrenoceptor antagonists ('adrenergic binding site') while the other appears to be specific to idozoxan ('non-adrenergic binding site'). Indole alkaloids and imidazolines have different binding affinities for these, 'adrenergic' and 'non-adrenergic', receptors (Tibirica et al., 1991). However, differing binding affinities are only observed at concentrations of idozoxan much lower than those used in these series of experiments. Therefore, the inability of idozoxan to protect the ischemic myocardium is probably not due to the fact that it does not fully occupy the so called 'adrenergic sites' bound with high affinity by the indole alkaloids.

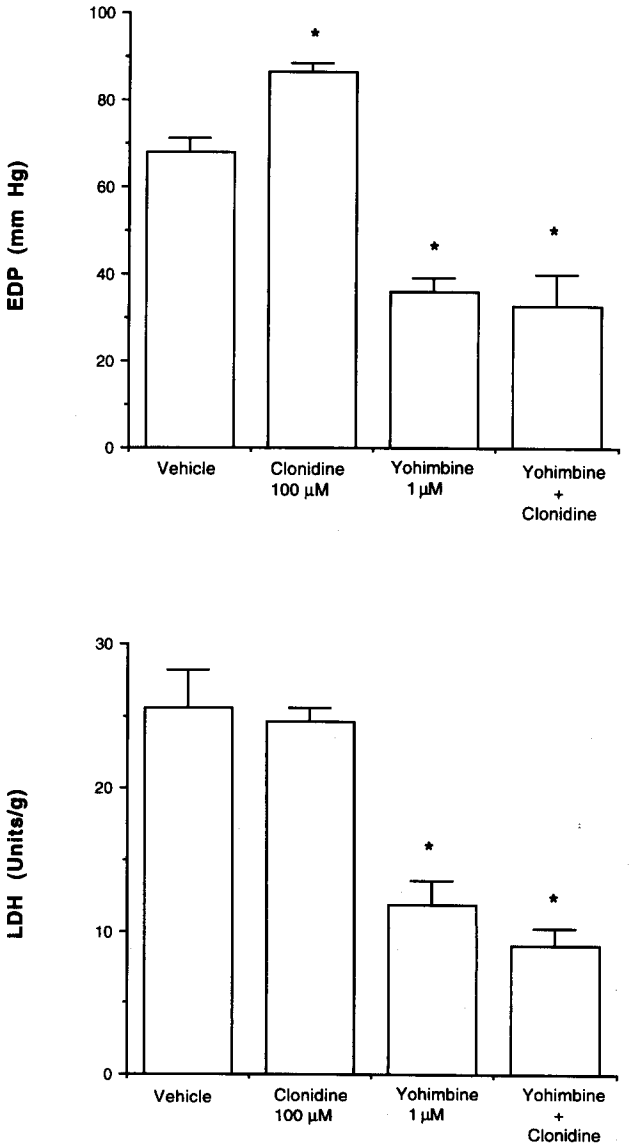

Fig. 2. The effect of clonidine in the presence or absence of yohimbine on EDP and cumulative LDH release at 30 min into reperfusion following 25 min global ischemia in isolated rat hearts. Hearts treated with yohimbine in the presence or absence of clonidine significantly reduced both EDP and LDH release (* $P < 0.05$).

Table 4
Effect of 5-HT in the absence or presence of yohimbine on cardiac function and coronary flow

	Pre-ischemia		30 min post reperfusion
	Pre-drug	Post-drug	
HR (beats / min)			
Vehicle	285 ± 6	281 ± 8	235 ± 17 [a]
30 μM 5-HT	273 ± 7	305 ± 5	222 ± 28
10 μM yohimbine	283 ± 4	74 ± 6 [a,b]	264 ± 3
10 μM yohimbine + 30 μM 5-HT	265 ± 17	146 ± 21 [a,b]	234 ± 30
LVDP (mm Hg)			
Vehicle	134 ± 2	125 ± 3	23 ± 4 [a]
30 μM 5-HT	140 ± 9	93 ± 10 [a,b]	19 ± 3 [a]
10 μM yohimbine	136 ± 6	104 ± 5 [a,b]	101 ± 3 [a,b]
10 μM yohimbine + 30 μM 5-HT	150 ± 5 [b]	98 ± 2 [a,b]	48 ± 3 [a,b]
Coronary flow (ml / min / g)			
Vehicle	21.4 ± 1.1	21.1 ± 1.1	15.0 ± 0.9 [a]
30 μM 5-HT	19.2 ± 1.0	15.9 ± 1.8 [a,b]	14.4 ± 1.0
10 μM yohimbine	18.0 ± 0.8	13.4 ± 1.0 [a,b]	15.5 ± 1.1
10 μM yohimbine + 30 μM 5-HT	18.5 ± 0.8	21.5 ± 1.5	12.4 ± 1.0 [a]

All values are means ± S.E.M., HR = heart rate, LVDP = left ventricular developed pressure. [a] Significantly different from its respective pre-drug value ($P < 0.05$). [b] Significantly different from its respective vehicle group value ($P < 0.05$).

Yohimbine protected ischemic myocardium in our model at equivalent concentrations to those found to protect the hypoxic myocardium (Takeo et al., 1991). The cardioprotection appears to be common to indole alkaloids as another structurally similar compound, rauwolscine also protected the ischemic myocardium. The recovery of reperfusion LVDP after yohimbine pretreatment is better than we have observed in this experimental model with most other anti-ischemic agents tested (Grover et al., 1993; Sargent et al., 1991). At the highest concentration tested, 10 μM, yohimbine caused significant pre-ischemic bradycardia and cardiodepression. Bradycardia is something that is expected after treatment with an α_2-adrenoceptor agonist, not an antagonist. However, the bradycardiac activity at high concentrations is something previously observed in isolated rat hearts pretreated with 5-HT_2 antagonists (Grover et al., 1993). At the highest concentration tested, cardiodepression was observed with both indole alkaloids. Again, this was an unexpected activity for an α_2-adrenoceptor antagonist, but this has been previously reported by Takeo et al. (1991). Cardioprotection by yohimbine was also observed at concentrations which had no pre-ischemic actions.

To confirm if α_2-adrenoceptor antagonism was necessary for the cardioprotective activity of yohimbine we determined the effects of the α_2-adrenoceptor agonist clonidine on this activity. Intravenous administration of clonidine causes a reduction in blood pressure and bradycardia. Previous reports have demonstrated that these effects of clonidine are primarily via activation of central α_2-adrenoceptors (Tibirica et al., 1991). In our experimental model in which central α_2-adrenoceptors are not present, we still observe bradycardia and significant pre-ischemic coronary vasoconstriction. Vasoconstriction is presumably due to stimulation of postsynaptic vascular α_2-adrenoceptors. The bradycardiac action of clonidine mediated by stimulation of presynaptic α_2-adrenoceptors has been previously reported (De Jonge et al., 1982). Therefore, the peripheral bradycardiac activity of clonidine should be reversed by yohimbine. However, this was not the case, suggesting that the bradycardiac activity of clonidine under these particular experimental conditions does not involve α_2-adrenoceptors. Although clonidine caused some pro-ischemic activity it did not reverse the cardioprotective activity of yohimbine. These findings suggest that α_2-adrenoceptor antagonism is probably not responsible for the protective effects of yohimbine observed in this experimental model.

Yohimbine is known to have several other activities, one of which is 5-HT receptor antagonism (Goldberg and Robertson, 1983; Frankhuyzen and Mulder, 1982). Our laboratory has previously shown that 5-HT_2 antagonists can protect isolated perfused globally ischemic rat and marmoset hearts (Grover et al., 1993). Therefore, we initially determined whether 5-HT antagonism was responsible for the cardioprotection observed after pretreatment with yohimbine. If the cardioprotective activity of yohimbine was due to 5-HT receptor antagonism then, 5-HT should reverse the cardioprotection observed. Treatment with 5-HT, at a concentration which had no pro-ischemic activity when given alone, partially reversed the cardioprotection observed with yohimbine. These results suggest that the cardioprotection observed with the indole alkaloid α_2-adrenoceptor

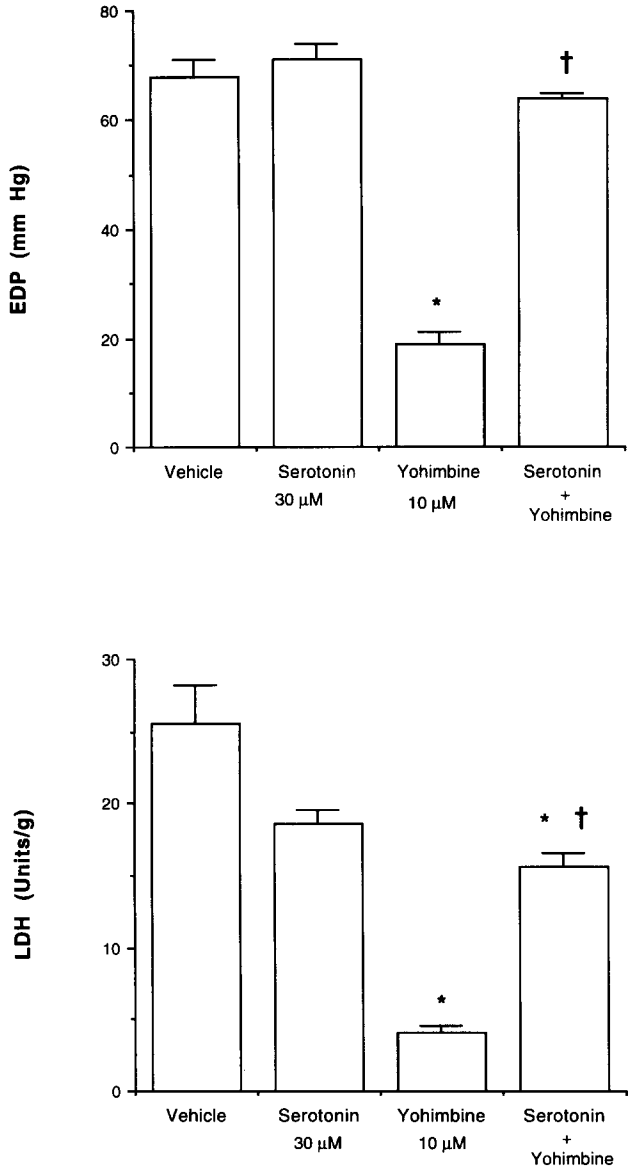

Fig. 3. The effect of 5-HT in the presence or absence of yohimbine on EDP and cumulative LDH release at 30 min into reperfusion following 25 min global ischemia in isolated rat hearts. Hearts treated with yohimbine in the absence of 5-HT significantly reduced both EDP and LDH release, significantly different from vehicle, * $P < 0.05$; significantly different from respective yohimbine alone, † $P < 0.05$).

antagonists are probably due to an antagonism of 5-HT receptors. The precise 5-HT receptor which is antagonized is unknown from these experiments. However, the ability of 5-HT_2 selective receptor antagonists to protect the ischemic myocardium suggests that this class of receptor may be important (Grover et al., 1993). At the present time, we do not know how blockade of 5-HT_2 receptors can cause cardioprotection, but an effect on intracellular calcium mobilization has been hypothesized (Grover et al., 1993).

In conclusion this series of experiments demonstrates that the indole alkaloid class of α_2-adrenoceptor antagonists protect the ischemic myocardium. This protective activity appears to be distinct from an ability to block α_2-adrenoceptors. Indeed, the results from these experiments suggest that an antagonism of 5-HT receptors is involved in the cardioprotective mechanism of action. However, other activities of the indole alkaloids may also contribute to the observed cardioprotection as serotonin only partially reverses the effects of yohimbine on reperfusion LVDP. Future studies will determine the involvement of other receptors, such as α_1-adrenoceptors in the cardioprotection of indole alkaloids.

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