Dexfenfluramine Elevates Systemic Blood Pressure by Inhibiting Potassium Currents in Vascular Smooth Muscle Cells

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ABSTRACT

Appetite suppressants, such as dexfenfluramine (dex), are associated with primary pulmonary hypertension, valvular heart disease, and systemic vascular complications, such as coronary, cerebral, or mesenteric ischemia. These drugs suppress appetite by enhancing release and inhibiting reuptake of serotonin in the central nervous system. The effects of dex on the systemic circulation have not been studied. K+ channels regulate vascular tone in most vascular beds. We hypothesized that dex is a systemic vasoconstrictor acting primarily by inhibiting K+ channels, independent of effects on serotonin. The effects of clinically relevant concentrations of dex (10^-6 to 10^-4 M) on outward K+ current and membrane potential were studied with whole-cell patch clamping in freshly isolated smooth muscle cells from rat renal, carotid, and basilar arteries. Tone was measured in tissue baths. Blood pressure, cardiac output, and left ventricular end diastolic pressure were assessed in open- and closed-chest anesthetized rats. At 10^-4 M, dex inhibits outward K+ current (50%) and increases membrane potential (by >35 mV), an effect comparable with 4-aminopyridine (5 mM). Furthermore, dex constricts rings and acutely elevates systemic pressure (+17 ± 3 mm Hg) and systemic vascular resistance in the presence of ketanserin. Dex vasoconstriction is dose-dependent (threshold dose 10^-6 M; 156 μg/ml) and enhanced in L-NAME-fed rats. We conclude that dex causes acicate systemic vasoconstriction, at least in part by inhibition of voltage-gated K+ channels, independent of effects on serotonin. To our knowledge, this is the first time that a commonly prescribed drug with voltage-gated K+ channel-blocking properties is shown to have significant hemodynamic effects in vivo.

Dexfenfluramine (dex) has been associated with the development of primary pulmonary hypertension (Abenhaim et al., 1996); systemic vascular complications such as coronary (Evraud and Allaz, 1990), cerebral (Schwitter et al., 1992), mesenteric (Schembre and Boynton, 1997), and digital ischemia (Marinella and Berretttoni, 1997); hypertension (Mabadeje, 1974); and most recently, fibrosis and insufficiency of cardiac valves (Connolly et al., 1997; Khan et al., 1988). Dex and fenfluramine (the d- and L-racemic mixture) are thought to suppress appetite by increasing the release and inhibiting the reuptake of 5-hydroxytryptamine (5-HT or serotonin) in the central nervous system (McTavish and Heel, 1992). However, the mechanism of the effects of these anorectic drugs on the vascular system has not been adequately studied. It is not known if dex's effects on the vasculature are mediated through 5-HT, or if another vasoconstrictor mechanism, independent of 5-HT, is involved. It has recently been shown that dex inhibits the outward K+ current (Ik) in pulmonary artery smooth muscle cells (Weir et al., 1996) as well as in cardiomyocytes of the rat (Hu et al., 1998). We hypothesized that dex constricts systemic arteries through inhibition of voltage-gated K+ channels (Kv) in systemic arterial smooth muscle cells (SASMC). The inhibition of Kv channels would cause depolarization and opening of the voltage-gated Ca2+ channels, increase in the intracellular Ca2+, and contraction.

We used the whole-cell patch clamp technique, isolated tissue baths, and in vivo experiments in closed- and open-chested rats. We show that dex inhibits a 4-aminopyridine (4-AP)-sensitive K+ current and depolarizes freshly dis-

ABBREVIATIONS: dex, dexfenfluramine; 5-HT, 5-hydroxytryptamine; Ik, outward K+ current; Kv, voltage-gated potassium current; SASMC, systemic arterial smooth muscle cells; 4-AP, 4-aminopyridine; NO, nitric oxide; NOS, nitric oxide synthase; L-NAME, L-NG-nitroarginine methyl-ester; LVEDP, left ventricular end diastolic pressure; CO, cardiac output; Alli, angiotensin II.
persed SASMC. Furthermore, dex constricts arterial rings and, at doses similar to those used in the treatment of obesity, dex acutely increases the systemic blood pressure and systemic vascular resistance in the anesthetized rat. These vasopressor effects are more pronounced in rats in whom nitric oxide (NO) synthesis has been inhibited and persist after the administration of ketanserin, an inhibitor with high affinity for the 5-HT2A and 5-HT2C receptor and lower affinity for the 5-HT2B Receptor (Awouters, 1985; Hoyer et al., 1994, Frishman et al., 1995), suggesting that dex’s effects on the vasculature are unrelated to serotonin and are counteracted by NO synthesis.

Materials and Methods

Artery Isolation and Cell Dispersion. Adult male Sprague-Dawley rats (250–350 g b.wt.) were euthanized with sodium pentobarbital overdose. The carotid, basilar, and third branch of the renal artery were removed, opened longitudinally, and kept in Ca2+−free Hanks’ solution (140 mM NaCl, 4.2 mM KCl, 1.2 mM KH2PO4, 1.5 mM MgCl2, 10 mM HEPES, 0.1 mM ethylene glycol bis(β-aminoethyl ether)-N,N,N′,N′-tetraacetic acid, pH 7.4) for 20 min. They were then placed in Hanks’ solution that contained 1 mg/ml papain, 0.75 mg/ml dithiothreitol, 0.8 mg/ml collagenase, and 0.8 mg/ml bovine serum albumin (all purchased from Sigma Chemical Co., St. Louis, MO) at 4°C for 15 min and then heated to 37°C for 10 min. The arteries were then transferred to iced Hanks’ solution and triturated with a Pasteur pipette. Dispersed SASMCs were transferred to the perfuson chamber on the stage of an inverted microscope for patch clamp studies.

Patch Clamping. Whole-cell patch clamp recordings were made as previously described (Weir et al., 1996). The microelectrodes had 1.5-mm o.d. and resistance of ~3 MΩ. The pipette solution contained 140 mM KCl, 1.0 mM MgCl2, 10 mM HEPES, 5 mM ethylene glycol bis(β-aminoethyl ether)-N,N,N′,N′-tetraacetic acid, and 10 mM glucose, pH 7.2. In some experiments amphotericin-perforated patches were used. The final concentration of amphotericin was 100 μg/ml pipette solution. The chamber containing the cells was perfused (2 ml/min) with a solution containing 145 mM NaCl, 5.4 mM KCl, 1.0 mM MgCl2, 1.5 mM CaCl2, 10 mM HEPES, and 10 mM glucose, pH 7.4 (extracellular solution). Cells were voltage-clamped at a holding potential of −70 mV and currents were evoked by 20-mV steps to −70 mV with test pulses of 200-ms duration at a rate of 0.1 Hz. Currents were filtered at 1 kHz and sampled at 2 kHz. Data were recorded and analyzed with pCLAMP 6.02 software (Axon Instruments, Inc., Burlingame, CA). Dextr and 4-AP were perfused in random order. Drugs were dissolved in the above-mentioned extracellular solution. 4-AP was first dissolved in normal saline and the pH was titrated to 7.4.

Isolated Tissue Bath. Rings with intact endothelium from rat carotid and renal (third branch) arteries were mounted on stainless steel wires (optimal resting tension to maximize constriction to 80 mM Eq KCl was 700 mg) and equilibrated for 30 min in a 4-ml bath containing Earle’s solution (pH 7.43, temperature 37°C, PO2 162 ± 5 mm Hg) as previously described (Archer et al., 1996). The rings were constricted with prostaglandin F2α (PGF2α; 5 x 10−4 M) to produce maximal constriction and then washed. In three PGF2α-preconstricted carotid and three PGF2α-preconstricted renal rings, the endothelial status was assessed with a dose response to acetylcholine (10−6, 10−5, and 10−4 M). Both carotid and renal rings dilated to 10−5 M acetylcholine. The constrictions to subsequent doses of dex were expressed as a percentage of the PGF2α constriction.

In Vivo Experiments. Rats were anesthetized with pentobarbital (40 mg/kg i.p.) and placed supine on a heated table throughout the experiment (rectal temperature 37°C). They were intubated via tracheostomy with an intramedic PE-280 tube (CMS; Curtin Matheson Sci., Houston, TX). For closed-chest rats, both the femoral veins were cannulated with intramedic PE-50 tubes for i.v. infusion of drugs. Drugs were infused at 500 μl/min with a syringe-infusion minipump system (pump22; Harvard Apparatus, South Natick, MA). The carotid artery was cannulated with an intramedic PE-50 tube and connected to a pressure transducer (Radnoti Glass Technology, Inc., Monrovia, CA). Recordings were made through an analog-to-digital converter (MacLab, Milford, MA). Two groups of rats were studied with the closed-chest model: control rats (n = 5) and NO synthase (NOS)-inhibited rats (n = 5). NOS inhibition was accomplished by adding L-Nω-nitroarginine methylester (L-NAME, 1.85 mM, Sigma Chemical Co.) to the drinking water for 4 days before the experiment, as previously described (Hampl et al., 1993). This achieves stable NOS inhibition throughout the 90 min of anesthesia, unlike acute administration that results in progressive increases in NOS inhibition. The closed-chest rats are stable, but do not allow measurements of left ventricular end diastolic pressure (LVEDP) and cardiac output (CO), which are necessary to rule out a direct effect of dex on the heart.

The open-chest rats allow measurements of LVEDP and CO and are stable, although the systemic blood pressure is lower than in the closed-chest rats. A thoracotomy was performed and a Doppler-flow probe placed around the ascending aorta to measure cardiac output (Ultrasonic blood flowmeter T101, 3S Flow mode; Transonic Systems, Inc., Ithaca, NY). LVEDP was measured by puncturing the left ventricle with a 21-gauge needle connected to a pressure transducer. Carotid artery pressure, LVEDP, and CO were simultaneously recorded.

The protocol of drug infusion was constant in all experiments, but the order of first administration of angiotensin II (AII) versus dex was randomized. All (10−6 M; 150 μl) was first infused, to assess the pressor effect of a vasoconstrictor with a different mechanism of action than dex and 4-AP. The effects of incremental doses of dex were then studied with equavolumetric boluses (40 μl) of dex 10−6, 10−5, and 10−4 M solutions (0.009, 0.092, and 0.920 mg dex/kg, respectively, in normal saline). After each dose was infused, the catheter was flushed with normal saline (40 μl). Ketanserin (40 μl of a 5 × 10−7 M solution in normal saline; ICN Nutritional Biochemicals, Cleveland, OH) or the 5-HT reuptake inhibitor fluoxetine (40 μl of a 10−4 M solution in normal saline; Research Biochemicals, Inc., Natick, MA), or vehicle (40 μl of normal saline), was then infused (n = 5 for each). If dex causes systemic vasoconstriction by releasing 5-HT, the constriction should be decreased by ketanserin and mimicked by fluoxetine. After ~15 min, the dex dose response was repeated. Finally, 4-AP (1 mM; 40 μl), an inhibitor of Kv channels, was infused. Approximately 1.5 min after the 4-AP injection, all rats developed seizures and were sacrificed with a pentobarbital overdose.

Statistics. All values are expressed as means ± S.E. Differences among multiple groups were calculated by ANOVA. A value of p < .05 was considered statistically significant. Post hoc analysis was performed with a Fisher probable least-significant difference test. Differences between two groups were calculated with Student’s paired t test.

Results

Whole-Cell Patch Clamp (Voltage Clamp). SASMCs from rat renal (third division, n = 6), carotid (n = 6), and basilar (n = 5) arteries were studied (Fig. 1, A–C). SASMCs were superfused with dex (10−4 M) or 4-AP (5 mM). We chose this dex concentration based on preliminary dose-response experiments, which showed that it inhibited ~50% of Ik in cells from all three arteries (at +70 mV). This effect is similar to that of 4-AP (5 mM), a preferential Kv channel blocker at this low concentration (Archer et al., 1996). Similar Ik inhibition was observed in amphotericin-perforated patches (where the cytoplasm of the SASMC is not dialyzed by the
pipette solution, allowing intact second messenger systems) on isolated renal artery (third division) SASMC. A dose response (10\(^{-6}\) to 10\(^{-4}\) M dex) at three different membrane potentials is shown in Fig. 2. Each cell was superfused with only one concentration of dex. After the threshold dose of 10\(^{-6}\) M, there was a larger decrease in Ik for higher concentrations of dex, at each membrane potential studied.

**Whole-Cell Current Clamp.** Renal artery SASMCs were superfused with incremental concentrations of dex (10\(^{-6}\), 10\(^{-5}\), and 10\(^{-4}\) M) (Fig. 3). Depolarization was concentration-dependent and was evident at 10\(^{-6}\) M. The 10\(^{-4}\) M dex significantly depolarized renal artery SASMC (Em = -51 \(\pm\) 7 mV; depolarization to -13 \(\pm\) 9 mV; n = 6). The 10\(^{-5}\) M dex did not cause any detectable depolarization (n = 2). The magnitude of depolarization to 10\(^{-4}\) M dex was similar to the depolarization caused by 5 mM 4-AP. In two experiments, 4-AP was superfused immediately after the 10\(^{-4}\) M dex without washout and caused no significant additional depolarization (Fig. 3).

**Isolated Tissue Baths.** Dex (10\(^{-4}\) M) constricted intact isolated rings from the rat carotid (n = 8) and renal (n = 9) arteries (Fig. 4). The carotid rings constricted to dex only after administration of L-NAME (10\(^{-5}\) M), whereas renal rings constricted significantly even without prior NOS inhibition.

**Closed-Chest Anesthetized Rats.** The L-NAME-fed rats had the expected increase in their baseline blood pressure (147 \(\pm\) 8 versus 132 \(\pm\) 9 mm Hg in the control group; p < .05). All caused reproducible increases in systemic blood pressure (Fig. 5) in both groups. Significant increases in blood pressure were caused by all three doses of dex, particularly in the L-NAME-fed rats (Figs. 5, 6A, and 7). The effects of dex were not altered by administration of ketanserin (40 \(\mu\)l of a 5 \times 10\(^{-7}\) M solution) (Fig. 6B). At this dose, ketanserin inhibited the increase in blood pressure caused by 5-HT (40 \(\mu\)l of a 10\(^{-4}\) M solution) (data not shown). Similarly, fluoxetine neither increased systemic blood pressure (at doses up to 10\(^{-4}\) M) nor altered the effects of the subsequently infused dex (Fig. 6B). In control rats, 4-AP (1 mM i.v.) increased systemic blood pressure (\(\Delta P\) = 21 \(\pm\) 5 mm Hg, n = 6; Fig. 5). The study of the hemodynamic effects of 4-AP was limited by the development of irreversible seizures 1.5 min after the injection into the rats, a reflection of the abundance of Kv channels in the central nervous system.

**Open-Chest Rats.** The same protocol was followed in open-chest rats. Dex, at all three doses, caused similar increases in the systemic blood pressure as in the closed-chest rats, but had no significant effects on LVEDP (6 \(\pm\) 4 mm Hg at baseline) and cardiac output (49 \(\pm\) 12 ml/min at baseline; Fig. 6C). The vasopressor effects of dex were, again, not attenuated by ketanserin.
The major finding of this study is that dex causes acute systemic vasoconstriction in vivo and ex vivo. This is associated with K⁺ channel inhibition and is not attenuated by the 5-HT receptor blocker ketanserin or mimicked by the 5-HT uptake inhibitor fluoxetine. Furthermore, the vasopressor effects of dex are more pronounced in L-NAME-fed rats [as in the pulmonary vasculature (Weir et al., 1996)], suggesting that endothelial dysfunction could be a risk factor for the vascular complications of dex. Endothelial dysfunction frequently coexists with the spectrum of diseases associated with obesity, such as hypertension and diabetes (Kirchner et al., 1993; Graier et al., 1996; Forte et al., 1997). We have recently reported NOS deficiency in humans with anorexia-induced hypertension years after discontinuation of the medication (Archer et al., 1998).

Dex inhibits Ik in SASMC from three different systemic arteries (Figs. 1 and 2) and this appears to be physiologically significant because it leads to membrane depolarization (Fig. 3). Dex inhibits Ik in amphotericin-perforated patches from third division renal artery smooth muscle cells. Ik at three different voltages is shown before (black columns) and after (pattern-filled columns) perfusion with dex. Each cell was superfused with only one concentration of dex. Values are means ± S.E. *p < .05.

**Fig. 2.** Dex inhibits Ik in amphotericin-perforated patches from third division renal artery smooth muscle cells. Ik at three different voltages is shown before (black columns) and after (pattern-filled columns) perfusion with dex. Each cell was superfused with only one concentration of dex. Values are means ± S.E. *p < .05.

**Fig. 3.** Dex causes membrane depolarization in renal artery smooth muscle cells. The effects of incremental concentrations of dex (10⁻⁶, 10⁻⁵, and 10⁻⁴ M) and 4-AP (5 mM) on the Em of a renal artery smooth muscle cells are exemplified in this representative trace. Dex causes depolarization at the low dose of 10⁻⁶ M, a dose similar to the therapeutic serum levels in humans. 4-AP perfused on top of 10⁻⁴ M dex does not cause significant further depolarization, suggesting that the two drugs might share a common mechanism of action, involving the inhibition of one or more K⁺ channels.

**Fig. 4.** Dex (10⁻⁴ M) constricts intact rings from the renal and carotid arteries. Percentage of maximal constriction to PGF₂α is shown in control and in rings previously treated with L-NAME. Note that the carotid rings constricted only after being incubated with L-NAME to inhibit NO synthesis. The renal rings constricted without any previous L-NAME treatment. Values are means ± S.E.
3). The fact that the low dose of $10^{-6}$ M dex causes significant depolarization, whereas it does not appear to significantly inhibit $I_k$ (Fig. 2), is not surprising. Due to the high input resistance of vascular smooth muscle cells (Nelson and Quayle, 1995), closure of very few $K^+$ channels might cause depolarization. The decrease in $I_k$ caused by the closure of a few channels is very small (in the order of a few pAs), and frequently below the sensitivity threshold of commonly used recording systems in whole-cell patch clamping. Dex and 4-AP result in similar magnitude depolarizations and when 4-AP is added to dex, there is no significant further depolarization (Fig. 3). This, along with the fact that dex inhibits the 4-AP-sensitive $I_k$ in several SASMCs (Fig. 1), suggests that dex and low-dose 4-AP might share a similar mechanism of action, involving inhibition of one or more Kv channels. Patel et al. (1997) have recently shown that dex ($10^{-5}$ M) inhibits a specific Kv channel, Kv2.1, expressed in Xenopus oocytes.

Although dex increases systemic vascular resistance (Fig. 6), which is controlled by small resistance arteries, it also constricts larger vessels, such as the carotid and third divi-
sion renal artery of the rat (Fig. 4). Although we cannot rule out that some 5-HT was released in the isolated tissue bath from nerve endings in the vessel wall, we speculate that the contraction to dex further supports a 5-HT-independent mechanism, possibly through K⁺ channel inhibition. Our findings are consistent with those of Coupar et al. (1969) who showed that fenfluramine causes contractions of isolated human gastrointestinal smooth muscle cells and postulated that fenfluramine had a direct effect on the cell’s membrane. Our conclusion also agrees with results obtained with dex in coronary artery rings (Desta et al., 1996). In that study, dex caused vasoconstriction at doses >10⁻⁶ M. This constriction persisted even after the rings were incubated with methiothepin, a 5-HT receptor blocker, suggesting a 5-HT-independent mechanism (Desta et al., 1996).

Although the carotid rings do not constrict to dex unless first incubated with L-NAME to inhibit NOS, the renal artery rings constrict to dex without pretreatment with L-NAME. This could be, at least in part, due to the fact that the contribution of NO in the control of vascular tone varies not only down the arterial tree but also among different vascular beds (Dahm et al., 1997). However, although both the preconstricted carotid and renal arterial rings dilated in response to acetylcholine, a wire-induced endothelial damage in the smaller renal rings also might contribute to the different responses of the renal and carotid rings. In agreement with our data, Desta et al. (1996) found that coronary rings constricted significantly more to dex if their endothelium was damaged with balloon denudation. Figure 5 shows that NOS inhibition in vivo caused a larger increase in the dex-induced vasoconstriction than in the AII- or 4-AP-induced vasoconstriction. This suggests that the enhanced pressor effect of dex in the L-NAME-fed rats is pressor-specific and not merely a reflection of a reduced initial arterial diameter (Nelin and Dawson, 1993). More studies will be needed to study the mechanism for this enhancement. Although we did not perform patch clamping in SASMC from L-NAME-fed rats, it is unlikely that the enhanced dex effects in these SASMC simply reflect a larger baseline K⁺ channel activity. Although it has been shown that, at least in the cerebral circulation, hypertension results in increased baseline activity of calcium-activated K⁺ channels (Liu et al., 1988), dex inhibits a 4-AP-sensitive Kv current and not the tetraethylammonium-sensitive calcium-activated K⁺ channel current (Fig. 1) (Weir et al., 1996; Patel et al., 1997; Hu et al., 1998). In addition, pulmonary (Yuan et al., 1998) and systemic (Takimoto et al., 1997) hypertension has been shown to induce a decrease rather than an increase in Kv channel activity.

Our in vivo experiments showed that dex increases systemic blood pressure at doses as low as 10⁻⁶ M (Fig. 7). This increase in pressure is not associated with changes in CO or LVEDP, suggesting that it reflects an increase in systemic vascular resistance rather than an effect on the heart (Fig. 6C). This is important because very recently Hu et al. (1998) showed that dex inhibits a Kv current in isolated rat right ventricular cardiomyocytes and therefore it could affect myocardial contractility by altering the duration of membrane potential. We postulate that the acute systemic vasoconstriction caused by dex is, at least in part, mediated by SASMC Kv channel inhibition and is independent of 5-HT (Fig. 6B). Celada et al. (1994) and Redmon et al. (1997) reported normal or low whole-blood levels of 5-HT in rats and patients taking dex, respectively. However, systematic studies assessing plasma levels, as opposed to whole-blood levels, of 5-HT in patients taking the drug with and without dex-induced vascular complications are lacking. Studies in rats fed with dex will be needed to determine whether other mechanisms involved in possible chronic effects of dex on the systemic vasculature.

Hypertension has been reported with the use of fenfluramine in humans. Mabadeje (1974) reported a significant increase in blood pressure in five patients, three of whom were on antihypertensive treatment, shortly after taking fenfluramine. Miezoch et al. (1979) studied the long-term effects of fenfluramine in the pig and reported an increase in the systemic blood pressure and systemic vascular resistance. Abenhaim et al. (1996) recently published the results of an international case-control study assessing the risk of primary pulmonary hypertension in patients taking anorectic agents, the most frequently used of which was dex. The patients taking anorectics were more likely to have systemic hypertension compared with controls (adjusted odds ratio of 2.1; 95% confidence interval 0.7–6). This is a provocative finding but did not reach statistical significance. The anorectic-using patients had lost ~10% of their weight, which should be associated with blood pressure decrease, not a tendency for hypertension.

Our study was designed to use doses of dex similar to those achieved in the treatment of obesity. Peak- and steady-state levels of dex (Cheymol et al., 1995) and fenfluramine (Hosain and Campbell, 1975; Innes et al., 1977; Pietrusko et al., 1982) ranging from 27 to 158 μg/l have been reported in humans (no significant difference in levels between control and obese patients). Assuming first-order kinetics in the rat (total blood volume is ~20 cc in a 300-g rat) our estimated
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serum levels at peak would be 156 μg/l, 1560 μg/l, and 15,600 μg/l for the three dex doses studied, respectively. Although the concentration of dex that the SASMCl are exposed to cannot be predicted, the lowest dex dose (10⁻⁶ M) that had definite electrophysiologic and hemodynamic effects was similar to the steady-state serum levels in humans. It has to be emphasized that the above-mentioned calculations were based on dex levels in healthy volunteers. Patients with dex-induced complications might have higher levels of the drug in their serum and such studies are lacking. Furthermore, the significance and the levels of the active metabolite nor-dexfenfluramine have not been adequately studied (Gibson et al., 1993). The rats that we studied were unselected and probably lacking the abnormalities that predisposed patients might have. Such predisposing factors, other than abnormalities in the metabolism of the drug, could be endothelial dysfunction (Forte et al., 1997) and/or potassium channel abnormalities (Liu et al., 1988; Martens and Gelband, 1998).

In summary, we show that dex, at doses similar to the steady-state serum levels achieved in humans, causes acute systemic vasoconstrictor in unselected rats. This vasoconstriction appears to involve, at least in part, inhibition of one or more Kv channels in SASMCl. We propose that NO deficiency could be a significant risk factor for the development of dex-induced vascular complications. Sibutramine, an anorexin with a similar to dex mechanism of action, was approved by Food and Drug Administration for the treatment of obesity in December 1997 (Heal et al., 1998; McNeely and Goa, 1998; Van Gaal et al., 1998). The American Heart Association recently urged physicians and the public to be cautious in the use of sibutramine, given the high incidence of systemic hypertension associated with its use (American Heart Association, 1998). Potential effects of sibutramine and other anorexigens on vascular K⁺ channels and systemic hemodynamics need to be carefully studied.

References


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