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Short communication

Catecholamine release in human heart by bupropion

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Abstract

Although there are some data on the cardiovascular profile of bupropion, a non-nicotine-based pharmacotherapy for smoking cessation, detailed studies of its specifically cardiac effects are lacking. In particular, the direct action of this agent on human myocardial contractility is not known. Therefore, we investigated the effects of bupropion on human cardiac tissue in vitro. Our results suggest that bupropion exerts indirect sympathomimetic activity producing positive inotropic effects in human myocardium most probably by catecholamine release.

Keywords: Bupropion; Heart; Contractility; Catecholamine; Amphetamine

1. Introduction

Cigarette smoking remains the major preventable cause of early morbidity and mortality. Until recently, the only specific pharmacotherapy available for tobacco dependence was nicotine replacement therapy. Even though this approach does increase long-term cessation rates, it is by no means a panacea for all smokers requiring help to quit. Bupropion is the first non-nicotine-based pharmacotherapy for smoking cessation and relative cessation rates in smokers taking bupropion are about double those seen with placebo (Hurt et al., 1997). Initially developed and marketed as an antidepressant, the exact mode of action of the drug still remains unclear after many years of study but is thought to have an unusual, not yet fully understood, noradrenergic link. The substance is chemically unrelated to tricyclic, tetracyclic, selective serotonin re-uptake inhibitor, or other known antidepressant agents. There is evidence that bupropion rather acts as a sympathomimetic amine by selective inhibition of norepinephrine and dopamine re-uptake with minimum effects of the recapture of serotonin, which does not inhibit the actions of monoamine oxidase. This indirect sympathomimetic property might be explained by its phenylethylamine-like molecular structure. In fact the molecular structure of bupropion and amphetamine both closely resemble that of phenylethylamine. Moreover, the major adverse effects of bupropion seem to be similar to those of appetite-suppressant amphetamines, including insomnia, weight loss and hypertension. In particular, cardiovascular side effects of bupropion treatment include blood pressure changes such as hypotension, orthostatic drop and especially exacerbation of hypertension. Also conduction disturbances and worsening of angina are known (Roose, 2000). Severe conduction delays (Paris and Saucier, 1998) and even myocardial infarction (Pederson et al., 2001) have been associated with ingestion of bupropion.

As these observations date from very small studies or even case reports, it is still unknown whether bupropion is detrimental or safe for patients with preexisting heart disease. Especially the cardiovascular effects of bupropion have not yet been assessed in patients with unstable heart disease or recent myocardial infarction, although detailed studies are ongoing (Holm and Spencer, 2000). The large number of patients receiving medical treatment for smoking cessation since 1997 in the USA and meanwhile throughout most of the European Union, in fact has prompted rising concerns and questions about bupropion triggering acute significant adverse events.

Detailed studies of the specifically cardiac effects of bupropion are lacking. In particular, the direct effect of this agent on human myocardial contractility is not known.

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Therefore, we investigated the direct effects of bupropion on human cardiac tissue in vitro.

2. Materials and methods

2.1. Human myocardial tissue

Experiments were performed on human right atrial trabeculae from nine patients obtained during open-heart coronary bypass surgery or heart valve replacement. Tissue pieces were suspended in ice-cold modified Bretschneider solution (containing in mmol/l: NaCl 15, KCl 9, $MgCl_2$ 4, histidine 180, tryptophane 2, mannitol 30, and potassium dihydrogen oxoglutarate 1) and were delivered immediately from the operation room to the laboratory.

2.2. Isolated cardiac muscle strip preparation and determination of force of contraction

Experiments were performed on isolated, electrically driven human right atrial muscle strip preparations as described previously (Böhm et al., 1989). Muscles of uniform size (length 6–8 mm; diameter <1 mm) were dissected under microscopic control and mounted individually in an organ bath containing 75 ml modified Tyrode's solution of the following composition (in mmol/l): NaCl 136.9, KCl 5.4, $MgCl_2$ 1.05, $CaCl_2$ 1.8, $NaHCO_3$ 22.6, NaH_2PO_4 0.42, glucose 5.0, ascorbic acid 0.28, EDTA 0.05; maintained at 37 °C and aerated continuously with carbogen (95% O_2 and 5% CO_2, pH 7.4). Each muscle was stretched to the length at which force of contraction was maximal (5–8 mN). Muscles were electrically stimulated by a FMI stimulator (FMI, Föhr Medical Instruments, Seeheim, Germany) (frequency 1 Hz; impulse duration 5 ms; intensity 10–20% greater than threshold). The developed tension was measured isometrically with an inductive force transducer and analyzed using the VitroDat Software (FMI, Föhr Medical Instruments). Concentration–response-curves were recorded after cumulative addition of the compounds, each being added when the maximum effect had been produced by the previous concentration. Since the compounds were mostly compared in tissue samples from the same hearts, there were no significant differences between the groups concerning i.e. age, sex and medication. Basal force of contraction was 3.2 ± 0.5 mN for bupropion, 2.8 ± 0.7 mN for bupropion and bucindolol, and 2.8 ± 0.9 mN for bucindolol, respectively.

2.3. Statistics

The data shown are means ± S.E.M. Statistical significance was estimated with Student's *t*-test for unpaired observations and analysis of variance (ANOVA). A *P* value of less than 0.05 was considered significant.

3. Results

Addition of increasing concentrations of bupropion (1–30 μmol/l) exerted a *positive* inotropic response in a concentration-dependent manner being significant above 30 μmol/l (maximal $44.8 \pm 17.8\%$ in the presence of 30 μmol/l bupropion, $n = 10$, $P < 0.05$) (Fig. 1, left panel).

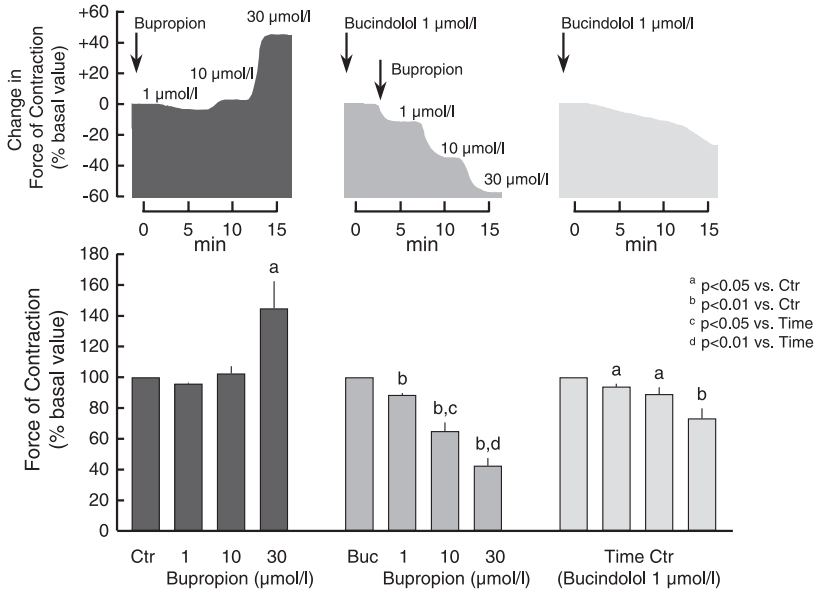

Fig. 1. Bar graph shows force of contraction in human right atrial trabeculae after application of bupropion (1–30 μmol/l) (left panel) and after application of bupropion (1–30 μmol/l) in the presence of bucindolol (1 μmol/l) (centre panel). The right panel shows the time control after application of bucindolol (1 μmol/l) (right panel). Force of contraction is given as percentage of basal value. Upper panels show corresponding original tracings illustrating the change in force of contraction (given as percentage of basal value) after application of the various compounds.

Interestingly, in the presence of the β-adrenoceptor antagonist bucindolol (1 μmol/l) addition of bupropion (1–30 μmol/l) led to a pronounced *negative* inotropic effect in a concentration-dependent manner (maximal $-57.5 \pm 5.0\%$ in the presence of 30 μmol/l bupropion, $n=16$, $P<0.01$) (Fig. 1, centre panel). Bucindolol was choosen as a β-adrenoceptor antagonist in this in vitro study because of its pharmacologic profile with comparable high intrinsic activity (Maack et al., 2000) with only minor negative inotropic effects (maximal $-26.7 \pm 6.7\%$ in the presence of 1 μmol/l bucindolol, $n=5$, $P<0.01$) (Fig. 1 right panel). Whether this comparable high intrinsic activity may have contributed to the lack of benefit provided by this agent in the BEST-trial (Bristow, 2000) remains to be further elucidated.

As expected, addition of the β-adrenoceptor agonist isoprenaline (0.01 nmol/l to 1 μmol/l) to the organ bath led to a concentration-dependent increase in force of contraction. However, no significant rightward shift was observed after pretreatment with bupropion (30 μmol/l) (not shown).

4. Discussion

Our results suggest for the first time that bupropion exerts positive inotropic effects in human myocardium. This action is most probably mediated by catecholamine release due to indirect sympathomimetic properties as bupropion bases on an amphetamine-like molecular structure. Interestingly, bupropion exhibits also negative inotropic properties revealed when cardiac β-adrenoceptors are blocked. The pathway involved in the latter effect remains unclear and might be due to toxic effects. However, the negative inotropic action of bupropion may also be related to an inhibition of calcium release from sarcoplasmic reticulum and by blocking calcium influx across the sarcolemma. This biphasic effect on myocardial contractility is already known from cocaine (Yuan and Acosta, 1994). One might speculate whether the cardiodepressive effect of bupropion might even be mediated by intrinsic activity at the β-adrenoceptor. As we did not observe any alteration of the concentration–response curve of the β-adrenoceptor agonist isoprenaline in the presence of bupropion, this signal-transduction pathway seems rather unlikely.

Following oral administration of bupropion to healthy volunteers, the mean C_{max} following a 150 mg dose every 12 h is 136 ng/ml (0.5 μmol/l) at steady state (Zyban product information, 1997). However, peak plasma concentrations of hydroxybupropion (one of three active metabolites) are approximately 10 times the peak level of the parent drug at steady state. The AUC at steady state is about 17 times that of bupropion. This may be of clinical importance as the inotropic properties of bupropion observed in this study in vitro might occur within the physiological concentration range in vivo since the plasma concentrations of the metabolites are higher than those of bupropion.

What is more, as bupropion is primarily metabolized by the cytochrome P450 2B6 (CYP2B6) isoenzyme, the potential exist for drug interactions with drugs that affect the CYP2B6 isoenzyme metabolism. Hence, the inotropic properties of bupropion may be detrimental especially in patients with preexisting heart disease. As a variety of medications used in the treatment of cardiovascular diseases (such as antiarrhythmics and β-adrenoceptor antagonists) are metabolized via this pathway, we hypothesize that a synergistic combination with bupropion might induce or deteriorate cardiovascular adverse events.

In conclusion, it is premature to conclude that bupropion is a ‘safe’ treatment in patients with heart disease. Thus, potential adverse effects and drug interactions should contraindicate the use of bupropion by patients with a history of cardiovascular disorders until further notice. In practice, when someone needs drug support to quit smoking, nicotine replacement therapy should be tried first.

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