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β-adrenoceptor responses to inhaled salbutamol in the elderly

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The purpose of the present study was to evaluate and compare the responsiveness of β_2-adrenoceptors in elderly and young subjects. Seven healthy elderly volunteers (72 ± 3 years) were given cumulative doses of inhaled salbutamol (100 μg–4000 μg) or placebo, following pre-treatment with propranolol 40 mg or placebo. Finger tremor (Tr), plasma potassium (K), and heart rate (HR) were measured at each dose step. There were dose-dependent increases in Tr ($P < 0.001$) and HR ($P < 0.001$) and falls in K ($P < 0.001$), which were completely attenuated by propranolol ($P < 0.001$). Comparison with dose-response curves in a group of young (Y) subjects (24 ± 3 years) given an identical dose protocol of salbutamol showed no evidence of subsensitivity of β_2-adrenoceptor responses in the elderly (E) group (mean and 95% confidence intervals for maximum responses): △K −0.90 (−1.1–−0.82) mmol l^{-1} Y, −0.82 (−1.04–−0.60) mmol l^{-1} E, △ Tr 274 (213–335)% Y, 269 (197–342)% E, △HR 25 (21–28) beats min^{-1} Y, 26 (21–31) beats min^{-1} E.

Keywords age β-adrenoceptor salbutamol propranolol

Introduction

The ageing process is accompanied by diminished sensitivity to several hormones. In particular, alterations occur in the adrenoceptor-adenylate cyclase system, with raised levels of plasma catecholamines in the elderly (Krall *et al.*, 1981; Zeigler *et al.*, 1976). *In vitro* studies have shown attenuation of isoprenaline induced adenylate-cyclase activity in lymphocytes (Krall *et al.*, 1981). A reduction in the affinity (Feldman *et al.*, 1984), but not numbers (Abrass & Scarpace, 1981) of lymphocyte β-adrenoceptors occurs in elderly subjects, in addition to altered activity of the catalytic unit of adenylate-cyclase (Abrass & Scarpace, 1982).

However, few studies have evaluated the *in vivo* responses of β_2-adrenoceptors in the elderly. The chronotropic response to isoprenaline (a non-selective β-adrenoceptor agonist) is diminished in elderly subjects (Johansson & Hjalmarson, 1988; Van Brummelen *et al.*, 1981; Vestal *et al.*, 1979). The purpose of the present study was to evaluate the systemic β-adrenoceptor effects of inhaled salbutamol (a selective β_2-adrenoceptor agonist) given alone, and in conjunction with propranolol, in a group of healthy elderly subjects. A group of young subjects given an identical dose protocol of salbutamol (Lipworth & McDevitt, 1989) were used as a control for comparison of β_2-adrenoceptor responses.

Methods

Subjects

After approval of the local ethics committee, informed consent was obtained from all subjects. Seven healthy elderly volunteers were studied: age (mean ± s.e. mean) 72 ± 3 years (range 66–84 years). These subjects were recruited from a social club for the elderly run by

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the University of Dundee. All subjects were non-smokers with no history of airflow limitation, atopy, hypertension, ischaemic heart disease or cardiac arrhythmias. None had previously been taking β-adrenoceptor agonists or antagonists. One subject was taking ibuprofen for osteoarthritis. Seven healthy young subjects were recruited from a pool of normal volunteers: age 24 ± 3 years (range 18–39 years). All subjects had a normal screen including full cardiorespiratory examination, blood biochemistry and 12 lead electrocardiograph.

Protocol

Elderly subjects attended the laboratory between 09.00 h and 10.00 h. Dose-response studies were performed using inhaled salbutamol or placebo, on three occasions, separated by 1 week intervals. Using a randomised single-blind cross-over design, subjects were given the following treatment combinations: a) inhaled salbutamol plus placebo propranolol, b) inhaled salbutamol plus oral propranolol 40 mg, and c) double placebo. An identical dose protocol was used for the young group who were given either inhaled salbutamol or placebo in single-blind fashion, but no pretreatment with propranolol.

Two hours prior to each dose-response study, the elderly subjects had ingested tablets containing either propranolol 40 mg or identical placebo. On arrival at the laboratory, subjects were laid supine, and a cannula was inserted into an antecubital vein. This was kept patent with bolus injections of heparinised saline. During a 30 min run-in period, two venous blood samples were taken at 15 min intervals for measurement of plasma potassium (K), and the mean of these values was used as a baseline. During the run-in period, heart rate (HR), blood pressure (SBP and DBP) and finger tremor (Tr) were recorded at 1 min intervals, until readings had settled to their lowest level, at a true baseline. The mean of the four lowest consistent readings were then taken.

Dose-response curves were then constructed by administering cumulative doubling doses of inhaled salbutamol or identical placebo, given by a 750 ml pear shaped spacer device (Nebuhaler, Astra Pharmaceuticals, Kings Langley, UK). The spacer device was used so as to eliminate individual differences in inhaler technique. Cumulative doses were given every 20 min as follows: 100 μg, 200 μg, 500 μg, 1000 μg, 2000 μg, 4000 μg. Identical metered-dose inhaler canisters were used delivering placebo, salbutamol 100 μg or salbutamol 500 μg per actuation (Glaxo Group Research, Middlesex, UK). At each dose increment Tr, HR, SBP and DBP were measured using the mean of the four lowest consistent readings, each taken at 1 min intervals. Venous blood was also taken for assay of plasma K. The blood was immediately centrifuged and stored at −20° C.

Measurements

Postural finger tremor was measured with an accelerometer transducer (Entran Ltd, Ealing, UK) taped to the distal phalanx of the middle finger. Tremor was recorded for a 20 s period with fingers extended, the wrist in neutral position and the forearm supported by a splint. Results were stored on computer disc, and tremor power (> 2 Hz) was calculated by spectral analysis using autocovariance. HR, SBP and DBP were all measured using a semi-automated sphygmomanometer (Dinamap vital signs monitor, Critikon Inc, Tampa, Florida, USA), with the subject in the supine position. All blood samples were analysed in batches at the completion of the study, and all assays were performed in duplicate. An IL 943 Flame photometer (Instrumentation Laboratory Inc., Warrington, UK) was used to measure plasma K. The coefficients of variation (CV) for analytical imprecision (between and within assays) were 0.44% and 0.38% respectively. The normal reference range for our laboratory is 3.5–5.0 mmol l^{-1}.

Statistical analysis

All statistics were performed on 'Statgraphics' software programme (STSC software publishing group, USA). Comparisons were made by analysis of variance and Student's *t*-test. Linear regression analysis was performed by the least squares method. A probability value of less than 5% (two-tailed) was accepted as being significant for all statistical tests. Values are shown in the text as means and 95% confidence intervals.

Results

There were no significant differences in baseline values for any of the measured variables. The mean baseline HR was lower after pretreatment with propranolol (60 [53–68] beats min^{-1}) compared with placebo (68 [60–76] beats min^{-1}) although 95% confidence intervals showed considerable overlap.

There were no significant changes with inhaled placebo for any of the parameters. There were dose dependent β_2-adrenoceptor re-

sponses to salbutamol ($P < 0.001$) although a plateau in the dose-response curve was not reached within the dose-range (Figure 1a,b,c). These changes were completely attenuated by propranolol ($P < 0.001$). There were linear log-dose response relationships for Tr ($r = 0.68$, $P < 0.001$), K ($r = -0.77$, $P < 0.001$) and HR ($r = 0.77$, $P < 0.001$). There were also strong correlations between different β_2-adrenoceptor responses: K and HR ($r = -0.73$, $P < 0.001$), K and Tr ($r = -0.63$, $P < 0.001$), HR and Tr ($r = 0.85$, $P < 0.001$). Salbutamol caused a small fall in DBP compared with placebo ($P < 0.05$): −7(−11–−2) mm Hg. There was also a small rise in SBP: 10(3–18) mm Hg, although this was not significant. The fall in DBP was attenuated by propranolol ($P < 0.01$).

Dose-response curves for systemic β_2-adrenoceptor responses were not significantly different in the elderly and young subjects (Figure 2a,b,c). In particular, a plateau in the

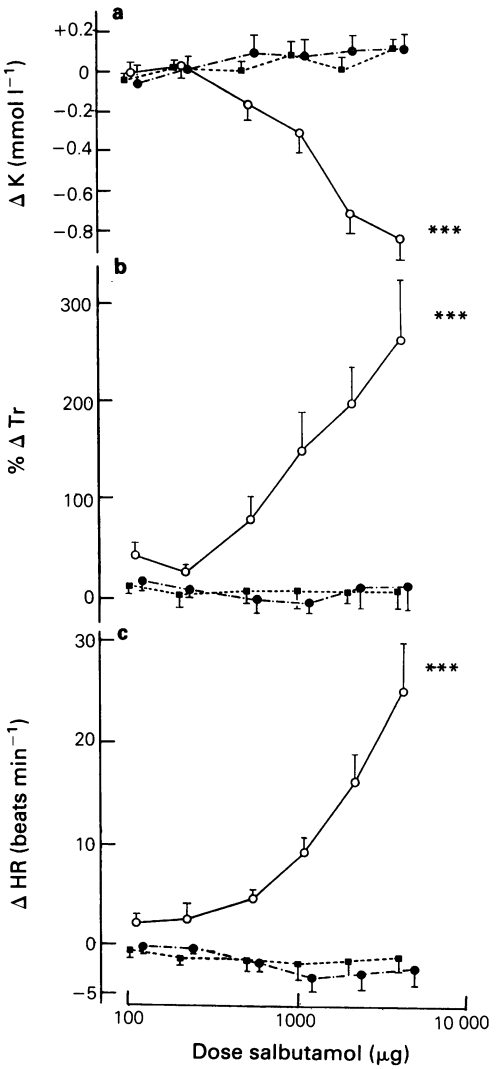

Figure 1 Cumulative log dose-response curves in seven elderly subjects for the response to inhaled salbutamol alone (○), inhaled salbutamol plus oral propranolol 40 mg (●), and placebo (■): for (a) hypokalaemia (K), (b) finger tremor (Tr), and (c) heart rate (HR). Values are shown as means and s.e. means (*** $P < 0.001$ by ANOVA).

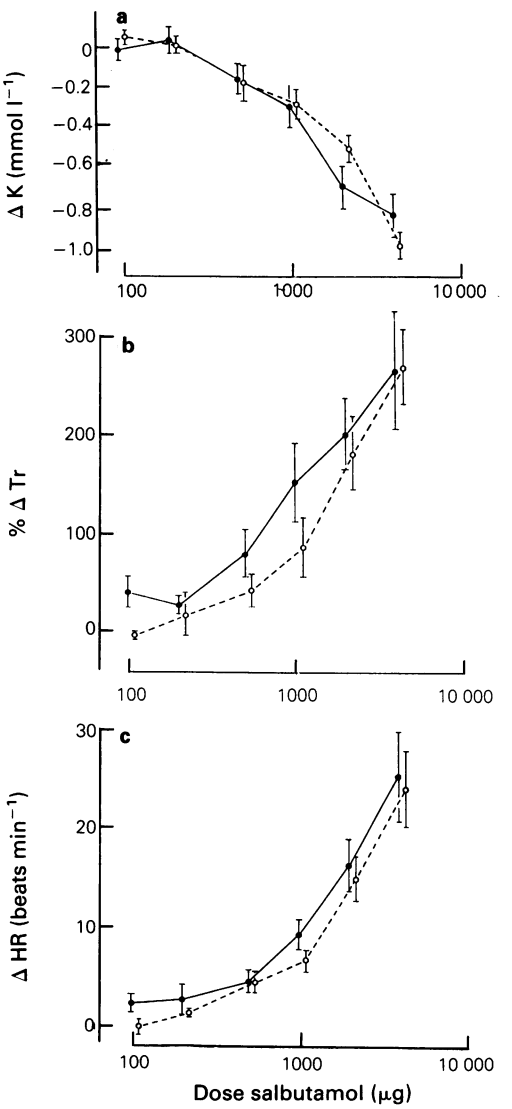

Figure 2 Comparison of β-adrenoceptor responses between seven elderly (—●—) and seven young (---○---) subjects for (a) hypokalaemic (K), (b) finger tremor (Tr) and (c) chronotropic (HR) effects. Values are shown as means and s.e. means.

dose-response curve was not attained and there were no significant differences between young (Y) and elderly (E) subjects for maximum responses to salbutamol: ΔK −0.90 (−1.1–−0.82) mmol l^{-1} Y, −0.82 (−1.04–−0.60) mmol l^{-1} E, ΔTr 274 (213–335)% Y, 269 (197–342)% E, ΔHR 25 (21–28) beats min^{-1} Y, 26 (21–31) beats min^{-1} E. Blood pressure responses were not compared because of absent or small changes in both groups.

Discussion

The results of the present study show that dose-related systemic β-adrenoceptor responses to salbutamol occur in healthy elderly subjects, which are attenuated by pre-treatment with propranolol. The dose-response curves for β_2-adrenoceptor responses (hypokalaemic, tremor and chronotropic) were similar in the young and elderly groups. The failure to detect a significant difference between young and elderly subjects may have reflected the large variance and type 2 statistical error, due to the small sample size used in the present study. Our findings may at first sight appear to conflict with previous studies showing subsensitivity of chronotropic responses in the elderly, in which isoprenaline was used as the β-adrenoceptor agonist (Johansson & Hjalmarson, 1988; Van Brummelen *et al.*, 1981; Vestal *et al.*, 1979). However, the situation may be more complex than was previously considered.

The hypokalaemic and tremor effects of salbutamol are known to be mediated by β_2-adrenoceptors (Lipworth & McDevitt, 1989). The chronotropic response to β-adrenoceptor agonists appears to be due to a combination of direct stimulation of β_1-adrenoceptors, reflex vagal withdrawal following β_2-adrenoceptor mediated vasodilatation, and also a direct effect on cardiac β_2-adrenoceptors (Arnold *et al.*, 1985; Bristow & Ginsburg, 1986). However, previous studies have shown that propranolol but not atenolol reduces the chronotropic effect of high doses of inhaled salbutamol (Lipworth *et al.*, 1989), and that vagal tone is reduced in the elderly (Dauchot & Gravenstein, 1971). Hence it seems likely that the dose-related salbutamol induced tachycardia seen in this study is predominantly generated through β_2-adrenoceptors.

The systemic responses induced by salbutamol in the elderly were comparable to those seen in younger subjects. Thus, in terms of tachycardia response, if the elderly are less sensitive to the effects of isoprenaline (a non-selective β-adrenoceptor agonist) but the effects of salbutamol (a selective β_2-adrenoceptor agonist) are unchanged, this may suggest that β_1-adrenoceptor responses are attenuated with preservation of β_2 responses. Such a conclusion would be supported by two other recent studies (Elfellah *et al.*, 1989; Klein *et al.*, 1988). Klein and co-workers (1988) have shown that β_2-adrenoceptor responses (peripheral vascular resistance and insulin release) to isoprenaline are unaffected by age, whereas the chronotropic response was reduced. Elfellah *et al.* (1989) have found that radioligand binding of β_2-adrenoceptors by (−)-[^{125}I] cyanopindolol in biopsies of skeletal muscle is also unaffected by ageing.

The heart rate response to exercise and its attenuation by β-adrenoceptor blockade are reduced in the elderly (Conway *et al.*, 1971): this is probably the most reliable indicator of cardiac β_1-adrenoceptor activity. If β_1-adrenoceptor activity does decline with age, leaving β_2 activity intact, it would appear to parallel the β-adrenoceptor changes which have been described in the failing human heart (Bristow *et al.*, 1986). Kendall and co-workers (1982) found blunting of cardiac but not metabolic responses to intravenous terbutaline in the elderly, and suggested that this may be due to a selective decline in β_1-adrenoceptor function. In contrast, Stressman *et al.* (1984) showed a reduction in plasma cyclic-AMP response to intravenous salbutamol in the elderly. However, their subjects were hospitalised and may therefore not be representative of the general ageing population. The use of intravenous as opposed to inhaled β-adrenoceptor agonist may account for differences in response compared with the present study.

In summary, our results showed no differences between β_2-adrenoceptor responses in the young and elderly. This may have been due to type 2 error, or alternatively due to the use of the inhaled as opposed to the intravenous route of administration. Studies are now indicated to assess whether airways effects of salbutamol mirror the responses of systemic β_2-adrenoceptors in the elderly.

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