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EFFECTS OF THE β-ADRENOCEPTOR ANTAGONISTS ATENOLOL AND PROPRANOLOL ON HUMAN WHOLE SALIVA FLOW RATE AND COMPOSITION

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Summary—The effects of β-adrenoceptor antagonists on salivary secretion have been extensively studied in animals but not in man. The aim here was to compare salivary flow rate and composition in man during 1 week of treatment with a non-selective (propranolol 80 mg b.i.d.) and a β_1-selective (atenolol 50 mg o.d.) antagonist with that of placebo. The randomized, double-blind, cross-over ("Latin square") design was used and 42 healthy male volunteers were recruited to the study. The treatment periods were separated by a wash-out period of 2 weeks. Whole saliva was sampled on day 0 (before) and on day 7 during each treatment. The plasma concentration of propranolol and atenolol was determined from blood samples obtained on day 7. Resting saliva was assessed for flow rate, amylase activity and concentration of total protein, hexosamine and sialic acid. Stimulated saliva was assessed for flow rate, pH, buffer pH, amylase activity and concentration of total protein, Ca^{2+}, Mg^{2+}, Na^+, K^+, Cl^- and PO_4^{2-}. In resting as well as stimulated whole saliva both the total protein concentration and the amylase activity were significantly decreased during the active treatment periods ($p < 0.05$–$p < 0.001$). At lunchtime during atenolol treatment the hexosamine/total protein and the sialic acid/total protein ratios were significantly increased ($p < 0.05$–$p < 0.01$), suggesting a possible effect on protein synthesis. In addition, the concentrations of Ca^{2+}, PO_4^{2-}, Cl^- and Mg^{2+} were significantly altered during the active treatment periods ($p < 0.05$–$p < 0.001$). The results suggested that the ductal Na^+ and Cl^- transport is under β-adrenoceptor control. Therapeutic doses of either the non-selective (propranolol) or the β_1-selective (atenolol) adrenoceptor antagonist thus significantly altered the composition of resting as well as stimulated whole saliva in healthy male volunteers, without affecting secretion rates.

Key words: atenolol, β-adrenoceptor antagonists, hypertension, propranolol, saliva composition, saliva secretion, side-effects.

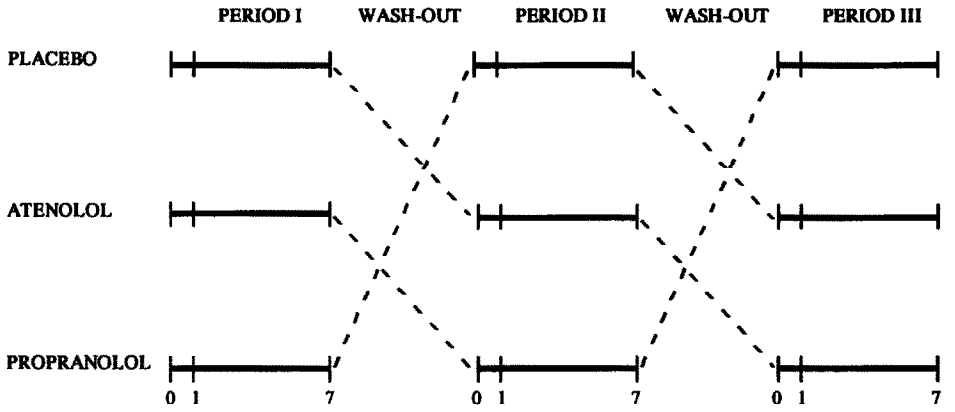
INTRODUCTION

In a previous study we have reported on the effects on whole saliva secretion of one of the first-line alternatives in the treatment of high blood pressure, the thiazide diuretic bendroflumethiazide (Nederfors, Twetman and Dahlöf, 1989). Another first-line antihypertensive treatment is β-adrenoceptor antagonists.

Most available β-blockers seem to be efficacious and well tolerated. However, there are differences between β-blocking agents regarding side-effects (Hansson, 1983). In about 15% of the patients the side-effects are so severe that they motivate re-evaluation of drug treatment (Report of Medical Research Council Working Party on Mild to Moderate Hypertension, 1981; Bai, Webb and Hamilton, 1982). The perceived side-effects may negatively influence the general quality of life of the patients (Croog *et al.*, 1986; Dahlöf and Dimenäs, 1990). One of the most frequently reported side-effects of treatment with β-adrenoceptor antagonists is gastrointestinal disturbance. The mouth constitutes the first part of the gastrointestinal tract, which makes it of interest to evaluate side-effects in this region, especially those concerning saliva production. The salivary gland cells are abundantly provided with β-adrenoceptors, mainly of the β_1-subtype (Carlsöö *et al.*, 1981; Schneyer and Humphreys-Beher, 1987; Iwabuchi, Aoki and Masuhara, 1988). β_2-receptors are present both in the glandular duct cells and in blood vessels of the salivary glands.

The effects of β-adrenoceptor antagonists have been extensively studied in different animal models, mostly using the rat. β-blocking agents have been shown to influence amylase activity (Olsen *et al.*, 1988), secretion of glycoproteins (Iwabuchi, Aoki and Masuhara, 1988) and proline-rich proteins (Johnson and Cortez, 1988; Watson *et al.*, 1990), and concentration of sodium and potassium (Jirakulsomchok and Schneyer, 1987a) as well as of calcium and phosphate (Schneyer, 1986; Ryberg *et al.*, 1989). Studies in man, however, are sparse. Parvinen, Parvinen and Larmas (1984) demonstrated that female patients taking β-blocking drugs had a significantly decreased flow rate of stimulated whole saliva. Laurikainen *et al.* (1988) showed an acute effect of the non-selective β-adrenoceptor antagonist timolol on both total protein concentration and amylase activity in parotid saliva in healthy volunteers.

Our aim now was to evaluate further possible effects on the flow rate and composition of whole saliva in man during treatment with the β_1-selective



DAY 0. Saliva sampling at 7.30-8.30 and 11.00-12.00 a.m. Baseline values.
DAY 1. Medication starts.
DAY 7. Saliva sampling at 7.30-8.30 and 11.00-12.00 a.m. Treatment values. Blood sampling at 10.00 a.m.

Fig. 1. 'Latin square' study design. The three different treatment periods are represented by horizontal bars and experimental days are indicated by vertical bars.

antagonist atenolol, the non-selective β-adrenoceptor antagonist propranolol or placebo in healthy male volunteers.

MATERIALS AND METHODS

Study design

a Forty-two healthy male volunteers were included. The mean age was 24 ± 4 yr, range 20–38 yr. During the tests, two of the subjects left the study because of severe, subjectively perceived side-effects, one during the atenolol and one during the propranolol treatment. Another two were excluded because they violated the protocol (zero drug-concentration in plasma). Thus, the final material consisted of 38 subjects.

The study had a randomized, double-blind cross-over ('Latin square') design (Fig. 1). The effect of atenolol (50 mg o.d. Tenormin®, ICI Pharmaceuticals) and propranolol (80 mg b.i.d. Inderal®, ICI Pharmaceuticals) was compared with that of visually identical placebo tablets. The tablets were taken at 7 a.m. and 7 p.m. on days 1–7. A double-dummy technique was used in order not to reveal any of the treatment alternatives. The treatment periods were separated by a wash-out period of 2 weeks.

Plasma concentrations of atenolol (β_1-selective) and propranolol (non-selective) were determined from blood samples taken at 10 a.m. on day 7 in each treatment period.

Saliva sampling and evaluation

Saliva was sampled before meals twice daily on days 0 and 7 in each treatment period, at 7:30–8:30 in the morning and at lunchtime (11:00–12:00). Unstimulated whole saliva was collected by passive drooling into ice-chilled test tubes during 5 min with the test subjects sitting in a relaxed position. Immediately afterwards, salivary secretion was stimulated by paraffin-chewing for 5 min. The saliva produced during the first 2 min was discarded and that produced during the following 3 min was collected in ice-chilled test tubes. Secretion rates were calculated by a gravitation method and expressed as ml/min.

Resting whole saliva was assessed for flow rate, amylase activity and concentration of total protein, hexosamine and sialic acid. For hexosamine and sialic acid, the relative share of total protein was also calculated. Stimulated whole saliva was assessed for flow rate, pH, buffer pH, amylase activity and concentration of total protein, calcium, chloride, magnesium, phosphate, potassium and sodium.

The pH value was immediately determined with a pH meter (PHI 61, Beckman Instr, Inc., Irvine, CA, U.S.A.). Buffer pH was determined according to Ericsson (1959). For unstimulated saliva one and for stimulated saliva two test tubes were immediately frozen and kept at $-70°C$ until further analysed.

Protein concentration was measured according to Lowry *et al.* (1951) using bovine plasma albumin as standard; amylase activity using the Phadebas® Amylase Test (Pharmacia Diagnostics, Uppsala, Sweden); hexosamine using a modified Elson–Morgan method (Blix, 1948); and sialic acid according to Warren (1959). Calcium, chloride, magnesium, potassium and sodium were measured by atomic absorption (Varian Techtron AA6, Varian Associates, Instrument group, Palo Alto, CA, U.S.A.). Chloride concentration was measured indirectly. Phosphate concentration was measured spectrophotometrically according to Murphey and Riley (1962). The chemical analyses were done at the Laboratory for Oral Biochemistry, University of Umeå, Sweden.

Statistical analyses

Statistical analyses were by Student's paired two-tailed t-test.

RESULTS

Resting and stimulated whole saliva secretion rates are presented in Table 1. The values given are the means of three different measurements (baseline

Table 1. Secretion rates (ml/min) for resting and stimulated whole saliva in healthy male volunteers ($n = 38$) at baseline in the morning and at lunchtime

		Mean ± SD
Resting	Morning	0.4 ± 0.2
	Lunch	0.5 ± 0.3
Stimulated	Morning	1.9 ± 1.1
	Lunch	2.3 ± 1.7

values in each treatment period). For both resting and stimulated secretion rate the lunchtime values were significantly ($p < 0.001$) higher than in the morning. There was no significant effect of drug treatment on either resting or stimulated flow rate.

Total protein concentration and amylase activity in resting whole saliva are presented in Table 2; the lunchtime values were about 15 and 35%, respectively, higher than in the morning.

During treatment with either atenolol or propranolol both total protein concentration and amylase activity was decreased as compared to base line (Table 2). This effect was more pronounced at lunchtime, especially during treatment with atenolol.

At lunchtime, during treatment with atenolol, there was a significant increase in the hexosamine/total protein ratio ($p < 0.05$) as well as in the sialic acid/total protein ratio ($p < 0.01$) in comparison to baseline (data not shown).

Total protein concentration and amylase activity in stimulated whole saliva are presented in Table 3. Also for stimulated whole saliva the lunchtime values were significantly higher (about 35 and 70%, respectively).

During treatment with either atenolol or propranolol the decrease in total protein concentration in stimulated saliva was even more pronounced than in resting saliva. Amylase activity showed a significant decrease during the active treatment periods. This effect was, however, complex (Table 3). Amylase act ivity was also significantly decreased by about 8% during treatment with placebo in comparison to baseline.

Mean values for sodium, potassium, calcium, phosphate, chloride and magnesium concentrations in stimulated whole saliva are presented in Table 4. During the different treatment periods, most electrolyte concentrations were affected. Sodium showed a decrease in concentration during treatment with placebo but an increase during active drug treatment. The potassium concentration was basically unchanged.

Regardless of treatment, there was a small increase in calcium concentration as compared to baseline. This increase was especially pronounced at lunchtime during propranolol treatment. For phosphate concentration the changes were in the opposite direction. Thus, during both atenolol and propranolol treatment there was a small but significant decrease in phosphate concentration.

Table 2. Total protein concentration and amylase activity in resting whole saliva in the morning and at lunchtime before (day 0) and during treatment (day 7) of healthy male volunteers ($n = 38$) with placebo, atenolol and propranolol

	Morning			Lunch		
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
Day 0						
Protein (mg/l)	1458 ± 697	1349 ± 692	1466 ± 730	1617 ± 670	1527 ± 559	1693 ± 687
Amylase (U/ml)	163 ± 153	130 ± 94	165 ± 171	313 ± 291	310 ± 277	291 ± 197

	Morning						Lunch					
	Placebo	p	Atenolol	p	Propranolol	p	Placebo	p	Atenolol	p	Propranolol	p
Day 7												
Protein (mg/l)	1489 ± 903	NS	1287 ± 625	NS	1395 ± 739	NS	1516 ± 512	NS	1305 ± 517	**	1477 ± 613	*
Amylase (U/ml)	132 ± 98	NS	104 ± 103	NS	98 ± 82	*	269 ± 197	NS	169 ± 155	***	215 ± 140	*

Statistical calculations (p) concern differences between baseline (day 0) and treatment (day 7) periods.
Significance levels $*p < 0.05$; $**p < 0.01$ and $***p < 0.001$. NS, Not significant.

Table 3. Total protein concentration and amylase activity in stimulated whole saliva in the morning and at lunchtime before (day 0) and during treatment (day 7) of healthy male volunteers ($n = 38$) with placebo, atenolol and propranolol

	Morning			Lunch		
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
Day 0						
Protein (mg/l)	836 ± 193	801 ± 215	802 ± 225	1086 ± 193	1108 ± 270	1104 ± 338
Amylase (U/ml)	199 ± 109	208 ± 141	208 ± 114	346 ± 196	362 ± 213	341 ± 167

	Morning						Lunch					
	Placebo	p	Atenolol	p	Propranolol	p	Placebo	p	Atenolol	p	Propranolol	p
Day 7												
Protein (mg/l)	818 ± 248	NS	695 ± 157	*	749 ± 198	*	1077 ± 323	NS	912 ± 337	***	978 ± 242	**
Amylase (U/ml)	180 ± 107	*	144 ± 109	**	163 ± 105	***	320 ± 182	*	285 ± 199	*	308 ± 178	*

Statistical calculations (p) concern differences between baseline (day 0) and treatment (day 7) periods.
Significance levels $*p < 0.05$; $**p < 0.01$ and $***p < 0.001$. NS, Not significant.

Table 4. Salivary electrolyte concentrations (mmol/l) in stimulated whole saliva in the morning and at lunchtime before (day 0) and during treatment (day 7) of healthy male volunteers ($n = 38$) with placebo, atenolol and propranolol

	Morning			Lunch		
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
Day 0						
Sodium	18.1 ± 10.8	16.8 ± 10.3	18.3 ± 11.3	16.5 ± 10.0	15.7 ± 10.6	16.7 ± 10.9
Potassium	17.9 ± 2.3	17.8 ± 2.3	17.6 ± 2.3	19.3 ± 2.5	19.4 ± 2.6	19.3 ± 2.5
Calcium	1.04 ± 0.21	1.06 ± 0.19	1.06 ± 0.21	1.06 ± 0.20	1.10 ± 0.23	1.07 ± 0.20
Phosphate	3.51 ± 0.77	3.39 ± 0.67	3.29 ± 0.57	3.54 ± 0.75	3.51 ± 0.65	3.59 ± 0.66
Chloride	20.6 ± 7.3	20.5 ± 7.7	21.0 ± 6.7	18.4 ± 6.6	18.1 ± 6.9	18.6 ± 6.5
Magnesium	0.13 ± 0.05	0.12 ± 0.05	0.12 ± 0.05	0.09 ± 0.03	0.09 ± 0.03	0.10 ± 0.04

	Morning						Lunch					
	Placebo	p	Atenolol	p	Propranolol	p	Placebo	p	Atenolol	p	Propranolol	p
Day 7												
Sodium	16.8 ± 10.9	NS	16.5 ± 9.4	NS	19.2 ± 11.4	NS	14.6 ± 9.4	*	17.2 ± 10.7	NS	18.2 ± 10.5	NS
Potassium	17.5 ± 2.5	NS	17.4 ± 2.1	NS	17.4 ± 2.3	NS	18.5 ± 2.5	*	18.8 ± 2.0	NS	18.9 ± 2.6	NS
Calcium	1.09 ± 0.23	*	1.12 ± 0.26	**	1.11 ± 0.23	*	1.08 ± 0.23	NS	1.12 ± 0.20	NS	1.15 ± 0.24	***
Phosphate	3.45 ± 0.75	NS	3.23 ± 0.56	*	3.15 ± 0.47	*	3.56 ± 0.83	NS	3.34 ± 0.78	NS	3.30 ± 0.65	*
Chloride	20.3 ± 7.5	NS	22.1 ± 7.0	NS	23.8 ± 8.8	**	17.1 ± 6.0	*	20.3 ± 6.2	**	21.7 ± 6.7	***
Magnesium	0.13 ± 0.06	NS	0.14 ± 0.05	**	0.13 ± 0.05	*	0.10 ± 0.04	NS	0.11 ± 0.04	**	0.11 ± 0.04	*

Statistical calculations concern differences between baseline (day 0) and treatment (day 7) periods.
Significance levels *$p < 0.05$, **$p < 0.01$ and ***$p < 0.001$. NS, Not significant.

The most significant effect on the electrolyte concentration of whole stimulated saliva, however, concerned chloride and magnesium. In comparison to baseline the concentrations of these ions increased significantly during the active treatment. For the chloride ion, this effect was more pronounced at lunchtime during both active treatments.

The mean plasma concentration for atenolol was 1232 nmol/l with a range of 113–3358 nmol/l and for propranolol 268 nmol/l with a range of 4–800 nmol/l. When, for each drug, the subjects were assigned to groups with either a low or high plasma concentration, the observed changes in amylase activity, total protein and electrolyte concentrations were more pronounced, in a statistically significant way, in the group with a high drug concentration.

DISCUSSION

Saliva secretion is controlled by both the parasympathetic and the sympathetic nervous systems. Fluid and salt secretion depends mainly on parasympathetic activity, whilst protein synthesis and exocytosis mainly depend on sympathetic activity. In this study, β-adrenoceptor blockade did not affect the salivary secretion rate but did significantly reduce both the total protein concentration and amylase activity in resting as well as stimulated whole saliva. Our results are thus in agreement with the above concept. Furthermore, they are in line with those of Laurikainen *et al.* (1988) but not with those of Parvinen *et al.* (1984). However, the decreased stimulated flow rate in the latter study was restricted to a small number of female patients ($n = 5$).

The effect on protein synthesis is somewhat surprising. Provided hexoseamine/total protein and sialic acid/total protein ratios are acceptable indicators of protein synthesis, the increased ratios during atenolol treatment could reflect a decreased excretion of non-glycosylated proteins. Johnsson and Cortez (1988), and recently Watson *et al.* (1990), describe an altered composition of proline-rich proteins in rat saliva during treatment with β-adrenoceptor antagonists. The human situation remains to be investigated. However, such changes may have an influence on both enamel pellicle and dental plaque formation (Hay, 1973; Kousvelari, Ciardi and Bowers, 1988) and thus be of importance for the maintenance of oral health. Interestingly, Watson *et al.* (1990) demonstrated an increased susceptibility to caries in rats during treatment with propranolol.

Jirakulsomchok and Schneyer (1984, 1987b) have demonstrated both β_1 and β_2-adrenoceptors in rat submandibular main duct. Our observations on changes in electrolyte concentration indicate that in humans also ductal modification of primary saliva electrolyte concentration is under β-adrenergic regulation. The increased chloride concentration is most likely explained by a reduced reabsorption because the salivary secretion rate is unchanged. In the duct system, the chloride ions are considered mainly to pass passively over the ductal cell membranes as a consequence of active transcellular sodium transport (Knauf *et al.*, 1982). Although sodium concentration was not significantly affected in our study, there was a close correlation between changes in chloride and sodium concentrations (Fig. 2), indicating an effect on ductal sodium transport. Our findings on changes in sodium and chloride concentrations are in accordance with observations by Schneyer and Thavornthon (1973) and Jirakulsomchok and Schneyer (1984, 1987b).

Studies in rats by Yu and Schneyer (1984), Schneyer, Yu and Jirakulsomchok (1985) and Schneyer (1986) demonstrate that calcium secretion is regulated by acinar β_1-adrenoceptors and that giving β-adrenoceptor antagonists results in decreased salivary calcium concentrations. In contrast we here demonstrate a slight but statistically significant increase in calcium concentration in human whole saliva during treatment with β-adrenoceptor antagonists. At present we have no obvious explanation for this. The other studies were, however, carried out in an animal experimental model in which selective

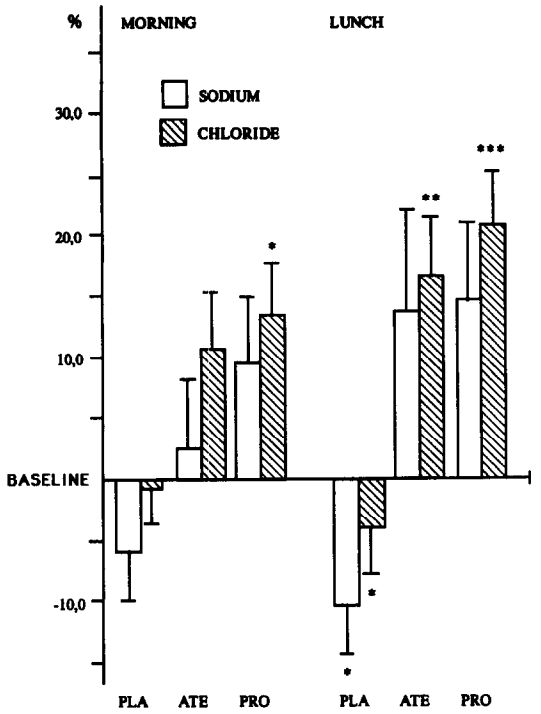


Fig. 2. Percentage difference in sodium and chloride concentrations in stimulated whole saliva between baseline (day 0) and treatment (day 7) of healthy male volunteers ($n = 38$) with placebo (PLA), atenolol (ATE) and propranolol (PRO). Error bars indicate SD.

adrenergic gland stimulation was accomplished either by direct stimulation of the sympathetic nerve or by giving adrenergic agonists. This selective adrenergic stimulation resulted in changes in both flow rate and calcium concentration. The effect on acinar calcium regulation was thus clearly demonstrated, while a possible ductal influence on calcium concentration similar to that of sodium and chloride ought to be further elucidated.

We also found a significant increase in magnesium concentration during the active treatments. To our knowledge, the site of magnesium secretion is not known and consequently neither is the nature of the β-adrenoceptor interaction. The increased magnesium concentration may, however, indicate a β-adrenoceptor-dependent ductal regulation of magnesium reabsorption, a hypothesis that deserves to be further evaluated.

As there seems to be a discrepancy in the distribution of β-adrenoceptors between the parotid and the submandibular glands, at least in the rat (Humphreys-Beher and Schneyer, 1986), we are now making a study, using the same experimental model as here to analyse the effects on secretion from human parotid and submandibular-sublingual glands.

The clinical significance of our findings needs to be further evaluated. A decrease in total protein concentration may be of limited importance *per se*. If, however, this decrease affects proteins with specific biological activities, e.g. proline-rich proteins, lysozyme or bacteria-aggregating glycoprotein (BAGP), the demonstrated effect may be of considerable importance for maintenance of oral health. Changes in electrolyte concentration may also be of importance for oral health, e.g. changes in calcium and phosphate concentration.

In this study we have used just one therapeutic dose of each of the investigated drugs. As, however, the biological response to drug treatment varies considerably from person to person the covariation between changes in the observed salivary parameters and low and high plasma drug concentration serves as an indicator that those changes may be dose dependent.

We have shown that treatment of healthy male volunteers with a β_1-selective or a non-selective β-adrenoceptor antagonist in therapeutic doses significantly affects the composition of both the resting and stimulated whole saliva, thus demonstrating a delicate interplay and a possible high vulnerability of the human salivary system.

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REFERENCES

Bai T. R., Webb D. and Hamilton M. (1982) Treatment of hypertension with beta-adrenoceptor blocking drugs. *Jl R. Coll. Phys., Lond.* **16,** 239–241.

Blix G. (1948) The determination of hexosamine according to Elson and Morgan. *Acta chem. scand.* **2,** 467–473.

Carlsöö B., Danielsson Å., Henriksson R. and Idahl L.-Å. (1981) Characterization of the rat parotid β-receptor. *Br. J. Pharmac.* **72,** 271–276.

Croog S. H., Levine S., Testa M. A., Brown B., Bulpitt C. J., Jenkins C. D. and Williams G. H. (1986) The effects of antihypertensive therapy on the quality of life. *N. Engl. J. Med.* **314,** 1657–1664.

Dahlöf C. and Dimenäs E. (1990) Side-effects of beta-blocker treatment as related to the central nervous system. *Am. J. Med. Sci.* **299,** 236–244.

Ericsson Y. (1959) Clinical investigations of the salivary buffering action. *Acta odon. scand.* **17,** 131–165.

Hansson L. (1983) Drug treatment in hypertension. In *Handbook of hypertension. Clinical Aspects of Essential Hypertension* (Ed. J. I. S. Robertson), Vol I, pp. 397–436 Elsevier Science Publishers B.V., Amsterdam.

Hay D. I. (1973) The interaction of human parotid salivary protein with hydroxyapatite. *Archs oral Biol.* **18,** 1517–1529.

Humphreys-Beher M. G. and Schneyer C. A. (1986) β-adrenergic receptors and cAMP levels of rat parotid and submandibular glands during chronic isoproteronol treatment. *J. Auton. Nerv. Syst.* **17,** 263–271.

Iwabuchi Y., Aoki C. and Masuhara T. (1988) Effects of dobutamine and terbutaline on the secretion of glycoproteins from the acinar cells of the rat submandibular gland. *Jap. J. Pharmac.* **47,** 301–310.

Jirakulsomchok D. and Schneyer C. A. (1984) Effects of adrenergic agonists on electrolyte transport in perfused salivary duct of rat. *J. Auton Nerv. Syst.* **11,** 233–241.

Jirakulsomchok D. and Schneyer C. A. (1987a) Effects of α, β_1 and β_2 adrenergic antagonists on the Na and K concentrations of sympathetic-nerve stimulated rat saliva. *J. Auton Nerv. Syst,* **20,** 65–71.

Jirakulsomchok D. and Schneyer C. A. (1987b) Effects of sympathetic nerve stimulation in the presence of specific adrenergic antagonists on Na, K and Cl transport in perfused rat submandibular duct. *J. Auton. Nerv. Syst.* **19,** 255–259.

Johnson D. A. and Cortez J. E. (1988) Chronic treatment with beta adrenergic agonists and antagonists alters the

composition of proteins in rat parotid saliva. *J. dent. Res.* **67,** 1103–1108.

Knauf H., Lübcke R., Kreutz W. and Sachs G. (1982) Interrelationships of ion transport in rat submaxillary duct epithelium. *Am. J. Physiol.* **242F,** 132–139.

Kousvelari E. E., Ciardi J. E. and Bowers M. R. (1988) Altered bacterial aggregation and adherence associated with changes in rat parotid-gland salivary proteins induced *in vivo* by β-adrenergic stimulation. *Archs oral Biol.* **33,** 341–346.

Laurikainen K., Laurikainen E., Tenovuo J., Kaila T. and Vilja P. (1988) Effects of a β-blocking agent, timolol maleate, on saliva in healthy volunteers. *Scand. J. dent. Res.* **96,** 121–127.

Lowry O. H., Rosebrough N. R., Farr A. L. and Randall R. J. (1951) Protein measurement with the folin phenol reagent. *J. biol. Chem.* **193,** 265–275.

Murphy J. and Riley J. P. (1962) A modified single solution method for the determination of phosphate in neutral water. *Analytica. chim. Acta* **27,** 31–36.

Nederfors T., Twetman S. and Dahlöf C. (1989) Effects of the thiazide diuretic bendroflumethiazide on salivary flow rate and composition. *Scand. J. dent. Res.* **97,** 520–527.

Olsen P. S., Kirkegaard P., Rasmussen T., Magid E., Poulsen S. S. and Nexø E. (1988) Adrenergic effects on secretion of amylase from the rat salivary glands. *Digestion* **41,** 34–38.

Parvinen T., Parvinen I. and Larmas M. (1984) Stimulated salivary flow rate, pH and lactobacillus and yeast concentrations in medicated persons. *Scand. J. dent. Res.* **92,** 524–532.

Report of Medical Research Council Working Party on Mild to Moderate Hypertension (1981) Adverse reactions to bendrofluazide and propranolol for the treatment of mild hypertension. *Lancet* **12,** 539–543.

Ryberg M., Johansson I., Ericsson T., Mörnstad H., Henriksson R., Jönsson G. and Sundström S. (1988) Effects of chronic stimulation of salivary gland β-receptors on saliva composition and caries development in the rat. *J. oral path. Med.* **18,** 529–532.

Schneyer C. A. (1986) Calcium levels in rat submandibular gland and saliva after sympathetic nerve stimulation in the presence of α, β_1 and β_2-adrenergic antagonists. *Archs oral Biol.* **31,** 383–386.

Schneyer C. A. and Humphreys-Beher M. G. (1987) β-adrenergic and muscarinic receptor densities of rat submandibular main duct. *Proc. Soc. exp. Biol. Med.* **185,** 81–83.

Schneyer C. A., Yu J.-H. and Jirakulsomchok D. (1985) Modification of dobutamine- and terbutaline-induced calcium and fluid secretion from rat salivary glands by atenolol and butoxamine. *J. Auton. Nerv. Syst.* **13,** 275–285.

Schneyer L. H. and Thavornthon T. (1973) Isoproteronol-induced stimulation of sodium absorption in perfused salivary duct. *Am. J. Physiol.* **224,** 136–139.

Warren L. (1959) The thiobarbituric acid assay of sialic acids. *J. biol. Chem.* **234,** 1971–1975.

Watson G., Pearson S., Falany J., Tabak L. and Bowen W. (1990) The effect of chronic propranolol treatment on salivary composition and caries in the rat. *Archs oral Biol.* **35,** 435–441.

Yu J.-H. and Schneyer C. A. (1984) Effect of α- and β-adrenergic agonists on fluid and calcium secretion by rat salivary glands. *Archs oral Biol.* **29,** 141–146.