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Interaction Between Substance P and β-Adrenergic Agonists in the Modulation of the Secretion of Fluid and Protein by the Rat Submandibular Gland

YOSHIKI IWABUCHI AND TOMOHIKO KIMURA

Department of Dental Pharmacology, School of Dentistry at Niigata, The Nippon Dental University, Niigata, Niigata 951, Japan

Abstract

The interactions between substance P and β-adrenergic agonists such as isoprenaline, dobutamine and terbutaline in the control of the secretion of fluid and protein from the rat submandibular gland have been examined.

Substance P elicited large volumes of saliva whereas isoprenaline, dobutamine and terbutaline elicited small volumes only. The secretion of fluid in response to substance P was markedly enhanced when substance P was administered in combination with isoprenaline or dobutamine but not when it was administered in combination with terbutaline. Isoprenaline elicited large amounts of protein, whereas substance P elicited small amounts. The secretion of protein in response to isoprenaline did not change when isoprenaline was administered in combination with substance P. The secretion of fluid and protein induced by substance P in combination with isoprenaline was antagonized by metoprolol and by spantide, but it was unaffected by pretreatment with ICI118551.

These results suggest that in the rat submandibular gland stimulation of β_1-adrenoceptors but not of β_2-adrenoceptors potentiates the secretion of fluid that is induced by stimulation of tachykinin receptors, whereas stimulation of tachykinin receptors does not enhance the secretion of protein that is induced by stimulation of β_1-adrenoceptors.

Substance P is a tachykinin that is widely distributed in the central nervous system and in the peripheral fibres that innervate many tissues, including the salivary glands (Hökfelt et al 1977; Pernow 1983). When injected into rats this peptide induces secretion from the salivary glands of a large volume of saliva containing a relatively low concentration of protein (Martinez & Martinez 1981; Ekström et al 1983; Iwabuchi et al 1986; Ekström 1987).

The substance P-mediated secretion of fluid from rat submandibular glands is enhanced by pretreatment with calcitonin gene-related peptide (CGRP) (Ekström et al 1988), vasoactive intestinal polypeptide (VIP) (Iwabuchi & Masuhara 1994) and secretin (Iwabuchi & Masuhara 1994), all of which elevate intracellular levels of cAMP. However, the mechanism responsible for the modification of the effect of substance P by cAMP-elevating agents is unknown.

Correspondence: Y. Iwabuchi, Department of Dental Pharmacology, School of Dentistry at Niigata, The Nippon Dental University, 1-8 Hamaura-cho, Niigata 951, Japan.

Some information is available about the secretion of fluid and protein from rat submandibular glands in response to selective β_1 agonists (Ekström 1979; Schneyer et al 1985; Iwabuchi et al 1988) and selective β_2 agonists (Thulin 1972; Abe et al 1985; Schneyer et al 1985; Iwabuchi et al 1988). However, to the best of our knowledge there has been no systematic study of the effects of sequential stimulation of tachykinin and β_1- or β_2-adrenergic receptors on the secretion of fluid and protein.

This study was designed to examine the interaction between the selective β_1 agonist dobutamine, the selective β_2 agonist terbutaline, and the non-selective β-agonist isoprenaline and the effects of substance P in the modulation of the secretion of fluid and protein from the rat submandibular gland.

Materials and Methods

Animals

The study was performed with ten-week-old male Sprague–Dawley rats. A standard pellet diet (Oriental MF; Oriental Yeast, Osaka, Japan) and

water were freely available. The animals were fasted for 24 h before experimentation.

Drugs

Substance P and spantide were from The Peptide Institute (Osaka, Japan), (−)-isoprenaline hydrochloride from Sigma (St Louis, MO), dobutamine hydrochloride from Shionogi (Osaka, Japan), ICI118551 [*erythro*-DL-1-(7-methylindan-4-yloxy)-3-isopropylaminobutan-2-ol] from Zeneca (Macclesfield, UK), and terbutaline sulphate and metoprolol tartrate from Fujisawa (Osaka, Japan). All drugs were dissolved in physiological saline solution.

Evaluation of secretory response

Each animal was anaesthetized by intraperitoneal injection of pentobarbital sodium (50 mg kg^{-1}). The trachea was cannulated with a polyethylene tube (MRC; 2 mm i.d. × 2·7 mm; Makiguchi Gomu, Tokyo, Japan). The submandibular glands were exposed and separated from the adherent sublingual gland, the duct of which was ligated. Substance P (0·5 μg kg^{-1}) was injected intravenously. (−)-Isoprenaline, dobutamine or terbutaline (each 0·1 mg kg^{-1}) were separately injected intravenously. In some experiments, (−)-isoprenaline, dobutamine or terbutaline was injected intravenously 1 min before injection of substance P. Blocking agents, namely, the β_1-adrenergic antagonist metoprolol (1 or 5 mg kg^{-1}) or the β_2-adrenergic antagonist ICI118551 (1 or 5 mg kg^{-1}), were injected intravenously 20 min before injection of substance P and β-adrenergic agonists. The substance-P antagonist spantide (100 or 500 μg kg^{-1}) was injected intravenously only 30 s before injection of substance P. Submandibular saliva was collected with a capillary micro-pipette (Microcap; 20 μL; Drummond Scientific, Broomall, PA) from the oral opening of the submandibular ducts over intervals of 1 min for 10 min. Saliva from the parotid glands was absorbed with cotton. At the end of each experiment the submandibular glands were carefully removed and weighed. Flow rates were calculated from the volume of fluid per 100 mg wet weight of each gland. The submandibular saliva elicited during the 10-min period was pooled and the protein content was determined by the method of Lowry et al (1951) with bovine serum albumin as the standard.

Statistical analysis

Experimental data are expressed as means ± s.e.m. of results from eight animals. The significance of differences was determined by use of Student's *t*-test for unpaired observations.

Results

Sialogogic responses to substance P and to β-adrenergic agonists alone

The secretory response to intravenous injection of substance P at 0·5 μg kg^{-1} started after 10 s and lasted for approximately 3–4 min. The flow rates of saliva from rat submandibular glands during the first 3 min, from 0–1 min, from 1–2 min and from 2–3 min, after intravenous injection of substance P (0·5 μg kg^{-1}), were 6·06 ± 0·64, 0·69 ± 0·08 and 0·10 ± 0·04 μL per 100 mg wet weight, respectively (Figure 1). The total volume of saliva secreted in a 10-min period from the submandibular glands was 40·33 ± 4·66 μL (Table 1). Intravenous administration of (−)-isoprenaline, dobutamine or terbutaline (0·1 mg kg^{-1}) elicited secretion of saliva during the first minute. However, the time courses of the secretion of saliva differed significantly. The flow of saliva produced after administration of (−)-isoprenaline continued for 9–10 min, but secretion of saliva in response to dobutamine and to terbutaline ceased within approximately 2–3 min and

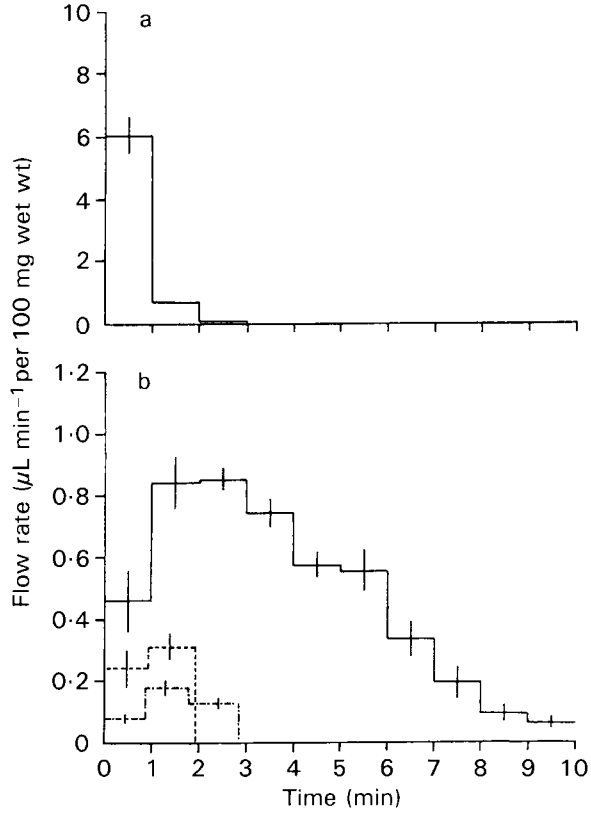

Figure 1. Effects of substance P (a) and β-adrenergic agonists (b) on flow rates of saliva from rat submandibular glands. Dobutamine (– – –), terbutaline (– · – · –) and isoprenaline (——), 0·1 mg kg^{-1}, were separately injected intravenously 1 min before intravenous administration of substance P (0·5 μg kg^{-1}). Data are the mean values of results from eight animals.

Table 1. Effects of dobutamine, terbutaline and isoprenaline on substance P-stimulated secretion of saliva by rat submandibular glands.

Treatment	Dose ($\mu g\ kg^{-1}$)	Total volume (μL in 10 min)
Substance P	0·5	40·33 ± 4·66
Dobutamine	100·0	2·99 ± 0·47
+substance P	0·5	53·55 ± 7·90
+substance P	0·5	43·32*
Terbutaline	100·0	2·07 ± 0·19
+substance P	0·5	37·29 ± 4·28
+substance P	0·5	42·40*
Isoprenaline	100·0	28·06 ± 2·03
+substance P	0·5	124·08 ± 8·73
+substance P	0·5	68·39*

Data are means ± s.e.m. Dobutamine, terbutaline and isoprenaline were injected separately, intravenously 1 min before intravenous administration of substance P. *The theoretical additive value is also shown for each experiment.

3–4 min, respectively (Figure 1). The total volumes of saliva secreted after administration of (−)-isoprenaline, dobutamine and terbutaline were 28·06 ± 2·03, 2·99 ± 0·47 and 2·07 ± 0·19 μL, respectively (Table 1).

Fluid secretion induced by the combination of substance P and β-adrenergic agonists

When rats were pretreated with (−)-isoprenaline, dobutamine or terbutaline at 0·1 mg kg^{-1}, salivation from the submandibular glands in response to substance P at 0·5 $\mu g\ kg^{-1}$ was observed for 7–8 min, 3–4 min and 2–3 min, respectively. Significant increases in the flow rate of saliva were noted with substance P and (−)-isoprenaline in combination from 0 to 3 min (data not shown). When rats were pretreated with (−)-isoprenaline or dobutamine the total volumes of saliva secreted from the submandibular glands after administration of substance P were 3·08-fold ($P < 0·001$) and 1·33-fold, respectively, greater than the volume secreted after administration of substance P alone. These volumes of fluid were greater than the volumes calculated as the theoretical additive responses. However, when rats were pretreated with terbutaline, the total volume of saliva secreted in response to substance P was similar to that secreted in response to substance P alone (Table 1).

The effects of various antagonists on the secretion of fluid induced by the combination of substance P and β-adrenergic agonists

The effects of metoprolol, ICI118551 and spantide on the volume of saliva induced in response to the

Table 2. Effects of metoprolol, ICI118551 and spantide on the secretion of fluid by rat submandibular glands in response to a combination of substance P and isoprenaline.

Treatment	Dose ($\mu g\ kg^{-1}$)	Total volume (μL in 10 min)
Isoprenaline	100·0	
+ substance P	0·5	124·08 ± 8·73
Isoprenaline	100·0	
+ substance P	0·5	
+ metoprolol	1000·0	94·08 ± 14·43†
+ metoprolol	5000·0	31·52 ± 2·89‡
Isoprenaline	100·0	
+ substance P	0·5	
+ ICI118551	1000·0	125·92 ± 6·31
+ ICI118551	5000·0	145·56 ± 12·70*
Isoprenaline	100·0	
+ substance P	0·5	
+ spantide	100·0	108·32 ± 4·12
+ spantide	500·0	53·39 ± 4·09‡

Data are means ± s.e.m. Metoprolol or ICI118551 was injected intravenously 20 min before intravenous administration of substance P and isoprenaline. Spantide was injected intravenously 30 s before intravenous administration of substance P. *$P < 0·05$, †$P < 0·01$, ‡$P < 0·001$, significantly different from the results obtained with the combination of substance P and isoprenaline alone.

combination of substance P and (−)-isoprenaline are shown in Table 2. After pretreatment with the β-adrenergic antagonist metoprolol at doses of 1 and 5 mg kg^{-1}, the volumes of saliva evoked by the combination of substance P and (−)-isoprenaline decreased by 24·2% ($P < 0·01$) and 74·6% ($P < 0·001$). In contrast, the volume was increased by 1·5% and 17·3% after pretreatment with ICI118551 compared with the volume secreted in response to the combination of substance P and (−)-isoprenaline alone. Rats were then pretreated with spantide at 100 and 500 μg kg^{-1}. After pretreatment with spantide at 100 μg kg^{-1}, the volume of saliva evoked by the combination of substance P and (−)-isoprenaline was significantly different, but the volume decreased by 57·0% ($P < 0·001$) when spantide was administered at 500 μg kg^{-1}. The effects of metoprolol and ICI118551 on the volume of saliva induced by the combination of substance P and dobutamine and by the combination of substance P and terbutaline are shown in Table 3. The volume of saliva evoked by the combination of substance P and dobutamine was reduced by 54·5% ($P < 0·01$) by pretreatment with metoprolol at 5 mg kg^{-1}. However, the volume of saliva evoked by the combination of substance P and terbutaline was unchanged by pretreatment with ICI118551 at 5 mg kg^{-1}.

The secretion of protein induced by the combination of substance P and (−)-isoprenaline

When rats were administered substance P (0·5 μg kg^{-1}) alone and (−)-isoprenaline (0·1 mg kg^{-1}) alone the concentrations of protein in saliva secreted during a 10-min period were 2·39 ± 0·28 and 50·39 ± 3·09 mg mL^{-1}, respectively (data not shown), and the total amounts of protein secreted in the saliva were 0·09 ± 0·01 and 1·40 ± 0·13 mg, respectively (Table 4). The concentration of protein in the saliva secreted in response to the combination of substance P and (−)-isoprenaline was 10·52 mg mL^{-1}. The total amount of protein secreted in response to the combination of substance P and (−)-isoprenaline was 1·29 ± 0·11 mg (Table 4). This amount was lower than the calculated theoretical additive response.

Effects of various antagonists on the secretion of protein induced by the combination of substance P and (−)-isoprenaline

The concentration of protein in saliva elicited by the combination of substance P and (−)-isoprena-

Table 3. Effects of metoprolol and ICI118551 on the secretion of fluid by rat submandibular glands in response to the combination of substance P and dobutamine or of substance P and terbutaline.

Treatment	Dose (μg kg^{-1})	Total volume (μL in 10 min)
Dobutamine	100·0	
+ substance P	0·5	53·55 ± 7·90
Dobutamine	100·0	
+ substance P	0·5	
+ metoprolol	5000·0	24·34 ± 2·05*
Terbutaline	100·0	
+ substance P	0·5	37·29 ± 4·28
Terbutaline	100·0	
+ substance P	0·5	
+ ICI118551	5000·0	44·80 ± 3·65

Data are means ± s.e.m. Metoprolol or ICI118551 was injected intravenously 20min before intravenous administration of substance P. *$P < 0·01$, significantly different from the result obtained with the combination of substance P and dobutamine.

Table 4. The total amounts of salivary protein secreted by rat submandibular glands in response to substance P and isoprenaline alone and in combination.

Treatment	Dose (μg kg^{-1})	Total amount (mg in 10 min)
Isoprenaline	100·0	1·40 ± 0·13
Substance P	0·5	0·09 ± 0·01
Isoprenaline	100·0	
+ substance P	0·5	1·29 ± 0·11

Data are means ± s.e.m. Isoprenaline was injected intravenously 1 min before intravenous administration of substance P.

Table 5. Effects of metoprolol, ICI118551 and spantide on the total amount of salivary protein secreted by rat submandibular glands in response to the combination of substance P and isoprenaline.

Treatment	Dose ($\mu g\ kg^{-1}$)	Total amount (mg in 10 min)
Isoprenaline	100·0	
+ substance P	0·5	1·29 ± 0·11
Isoprenaline	100·0	
+ substance P	0·5	
+ metoprolol	5000·0	0·18 ± 0·02*
Isoprenaline	100·0	
+ substance P	0·5	
+ ICI118551	5000·0	1·01 ± 0·10
Isoprenaline	100·0	
+ substance P	0·5	
+ spantide	500·0	0·70 ± 0·04*

Data are means ± s.e.m. Metoprolol or ICI118551 was injected intravenously 20 min before intravenous administration of substance P. Spantide was injected intravenously 30 s before intravenous administration of substance P. *$P < 0·001$, significantly different from the result obtained with the combination of substance P and isoprenaline.

line decreased by 45·1% ($P < 0·01$) after pretreatment with metoprolol at 5 mg kg^{-1} and by 34·0% ($P < 0·01$) after pretreatment with ICI118551 at 5 mg kg^{-1}; it did not change significantly after pretreatment with spantide at 500 $\mu g\ kg^{-1}$. The total amount of protein in saliva elicited by the combination of substance P and (−)-isoprenaline was reduced by 86·0% ($P < 0·001$) after pretreatment with metoprolol and by 45·7% ($P < 0·001$) after pretreatment with spantide, but it did not change significantly after pretreatment with ICI118551 (Table 5).

Discussion

In this study we found that the secretion of saliva from rat submandibular glands in response to substance P was markedly enhanced by pretreatment of the rats with the non-selective β-adrenergic agonist isoprenaline. The modulation by isoprenaline of the response to substance P was rapid, and significant increases in the flow rate of saliva were noted during the first minute of measurements. Martinez & Martinez (1981) showed that substance P inhibits the secretion of saliva in response to isoprenaline in the rat submandibular gland. These authors also showed that substance P does not block the binding of specific radioligands to β-adrenergic receptors in the submandibular gland. The potentiation by isoprenaline of the effect of substance P might, therefore, not be caused by interaction of the receptor level. We also found that the enhanced response was inhibited by pretreatment of rats with metoprolol and spantide but not by pretreatment with ICI118551. Metoprolol has been characterized as a β_1-adrenoceptor antagonist (Åblad et al 1975) and ICI118551 as a β_2-adrenoceptor antagonist (Bilski et al 1980). Spantide, (D-Arg[1], D-Trp[7,9], Leu[11])-substance P, has been shown to be a potent antagonist of tachykinin receptors and to inhibit the secretory responses induced by substance P alone in the rat submandibular gland (Bobyock et al 1986). These results suggest that, in respect of secretion of fluid, previous activation of β_1-adrenergic receptors increases the response mediated by the activation of tachykinin receptors.

The sialogogic activity of dobutamine, which has been characterized as a selective β_1-adrenoceptor agonist (Ruffolo et al 1981), was considerably lower than that of isoprenaline. In assays of β_1-adrenoceptor-mediated responses, such as assays of inotropic effects in the guinea-pig heart, the intrinsic activity of dobutamine was approximately 100-fold lower than that of (−)-isoprenaline (Maccarrone et al 1984). Thus, the smaller effect of dobutamine on the substance P-stimulated secretion of fluid might be attributable to its low intrinsic activity. In this study we found that the secretion of fluid in response to substance P was markedly enhanced by pretreatment of the rats with dobutamine, and the enhanced response was inhibited by pretreatment with metoprolol. However, the response to substance P and dobutamine was lower than that observed with the combination of substance P and isoprenaline. The total volume of saliva elicited in response to terbutaline, which has been characterized as a selective β_2-adrenoceptor agonist (Bergman et al 1969), was smaller than that elicited in response to dobutamine; this result is consistent with other reports (Schneyer et al 1985; Iwabuchi et al 1988). In binding studies butox-

amine, a selective antagonist of β_2-receptors, was found to have a lower capacity to antagonize binding of [^{3}H]dihydroalprenolol to a preparation of submaxillary gland membranes than the selective β_1-receptor antagonists butoxamine (Pointon & Banerjee 1979) and atenolol (Schneyer & Humphreys-Beher 1987). We also observed that terbutaline did not modify the secretion of fluid in response to substance P. In addition, the response to a combination of substance P and terbutaline was not inhibited by pretreatment of rats with ICI118551. It is possible that terbutaline has both β_1-adrenergic and β_2-adrenergic action in the rat submandibular gland, as indicated by observations of the release of amylase from the rat parotid gland (Suzuki & Ohshika 1985) and the secretion of fluid from the rat submandibular gland (Schneyer et al 1985; Iwabuchi et al 1988). Our results suggest that some β_2-receptors in the submandibular gland might not play a role in potentiating the substance P-mediated secretion of fluid. The potentiating effects of the three agonists tested were consistent with those reported by Miyamoto & Ohshika (1984) and Suzuki & Ohshika (1985), who found that the potency of β-adrenergic agonists with regard to the production of cAMP in rat parotid tissue was isoprenaline $\gg$ dobutamine $>$ procaterol. Larsson & Olgart (1989) reported that forskolin, which increases levels of cAMP via its action on adenylate cyclase, augments the carbachol-evoked secretion of fluid from the rat parotid gland. Thus, the potentiating effects seem to be mediated by intracellular messengers, such as cAMP.

The total output of protein from submandibular glands in response to isoprenaline was significantly higher than that in response to substance P. We also found that when isoprenaline was administered 1 min before substance P the amount of protein secreted in the saliva from submandibular glands was similar to that secreted after administration of isoprenaline alone. This observation is consistent with the report by Fleming et al (1984) that the secretion of mucin from dispersed cells of the rat submandibular gland in response to the combination of substance P and isoprenaline was identical with that in response to isoprenaline alone, when isoprenaline was added to the incubation medium 30 s before the addition of substance P. In the current study the secretion of protein induced by the combination of substance P and isoprenaline was significantly inhibited by spantide and metoprolol but not by ICI118551. Therefore, these results suggest that the stimulation of tachykinin receptors during activation of β_1-adrenergic receptors did not have any additive effects in terms of the secretion of protein.

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