Effects of Dopamine on the Secretion of Glycoproteins from the Functional Segments of the Rat Submandibular Gland

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Accepted June 22, 1987

Abstract—The action of dopamine (DA) on salivation and the secretion of marker glycoproteins (GP) from secretory cells of the rat submandibular gland (SMG) was investigated using various blockers at doses of 1 or 2 mg/kg (i.v.). DA at doses from 5 to 40 mg/kg (i.p.) dose-dependently increased salivation and the concentration of protein in SMG saliva. The order of inhibitory potency on salivation was propranolol (PPR) > phentolamine (PHN) > haloperidol (HAL) when DA was administered i.p. at a dose of 10 mg/kg and PHN > HAL > PPR when the dose of DA was 40 mg/kg. The concentration of protein in saliva after pretreatment with HAL or PHN increased significantly at a dose of 40 mg/kg of DA, but did not increase at a dose of 10 mg/kg of DA. Moreover, pretreatment with PPR decreased it at both doses of DA. The electrophoretic profiles of GP in DA-evoked saliva showed two characteristic main bands of GP I (130 KDa) and GP IV (21.5 KDa) contained in the acinar cells (AC) and a minor band of GP III (31 KDa) which originated from the granular tubular cells (GT). The profile was not changed by pretreatment with PHN and HAL when DA was administered at a dose of 10 mg/kg, but at a dose of 40 mg/kg, the intensity of band I increased. Pretreatment with PPR, when DA was administered at 40 mg/kg, caused an increase in the intensity of band III and a reduction in that of band I. These results suggest that DA, at low doses, affects the AC, whereas at a higher dose, it affects both the AC and GT.

The physiological role of dopamine (3,4-dihydroxyphenylethylamine), as a neurotransmitter, have been extensively investigated in the central nervous system (1, 2) and peripheral nervous system (3-6) in various mammalian species. Small doses of dopamine act as a pressor (7) and large doses act as a depressor (8) in the dog. In an electrophoretic study of rat submandibular saliva, Abe and Dawes showed that a small dose of dopamine elicited the secretion of some kinds of proteins which are characteristic of a response to \( \beta \)-adrenergic and cholinergic agonists, whereas large doses elicited secretion of proteins identical to those elicited by \( \alpha \)-adrenergic agonists (9).

We reported previously that the species of glycoproteins in the rat submandibular gland differ markedly between the acini and the granular convoluted tubules (10) and that species of glycoproteins characteristic of the acini are secreted into the saliva in response to \( \beta \)-adrenergic agents (11), cholinergic agents (12) and substance P (13), whereas glycoproteins characteristic of granular convoluted tubules are secreted in response to \( \alpha \)-adrenergic agents (11, 14).

The present study was carried out to elucidate the site of action of dopamine in the rat submandibular gland by comparing the electrophoretic profiles of the glycoproteins obtained from isolated functional segments of the gland with those in saliva elicited by treatment with dopamine alone or in combination with various blocking agents.

Materials and Methods
Collection of submandibular saliva: Male Sprague-Dawley rats, ten weeks of age, were
fasted but were given water ad libitum for the 24 hr prior to experimentation. Each rat was anesthetized with sodium pentobarbital (50 mg/kg, i.p.) and placed on a heating pad maintained at 37°C. The excretory ducts of the sublingual gland were ligated after they had been separated from the adherent tissues around the submandibular gland. The trachea was cannulated with a polyethylene tube (MRC, 2x2.7 mm). Submandibular saliva was then collected from the tip of the ductal cannula with a capillary micropipette (Drummond Microcaps, 10 and 20 μl) at intervals of 5 min until 30 min after the intraperitoneal administration of dopamine at doses of 5, 10, 20 and 40 mg/kg. Each of blocking agents was injected intravenously 30 min prior to the administration of dopamine (10 and 40 mg/kg, i.p.) at doses of 1 or 2 mg/kg. The total volume of saliva elicited per 5 min was measured, and then the saliva was promptly stored in small test tubes at -20°C until the assays were conducted. At the end of each experiment, the submandibular glands were carefully removed and flow rates were calculated from the volume of fluid elicited per minute per milligram of wet weight of each gland.

Preparation of functional segments: Parenchymal components from the rat submandibular gland were isolated by the method of Masuhara and Iwabuchi (10). Rats were anesthetized with pentobarbital and the submandibular gland was perfused via the carotid with a solution of collagenase which consisted of 0.1% collagenase (Sigma, Type II), 1.0 mM CaCl₂ and 0.1% bovine serum albumin in modified Hanks’ medium (137 mM NaCl, 5 mM KCl, 0.8 mM MgSO₄, 0.33 mM NaH₂PO₄, 0.44 mM KH₂PO₄, 1 mM MgCl₂, 10 mM Tris-HCl, pH 7.4). The submandibular gland was immediately removed, sliced, and then incubated for 120 min at 37°C in a sample of the same collagenase solution in an atmosphere of 95% O₂ plus 5% CO₂. The slices were rinsed with ice-cold modified Hanks’ solution to remove collagenase and then each segment of the acini and granular convoluted tubules was dissected out with needles, under a stereo-microscope.

SDS-polyacrylamide micro-disc electrophoresis: Each segment was dissolved in an equal volume of 6% (w/v) sodium dodecyl sulphate (SDS) solution which contained 10% 2-mercaptoethanol and then heated at 90°C for 3 min. The protein content of each of the samples of saliva and tissue was determined by the Lowry method (15) with bovine serum albumin as the standard. One μl of each sample, containing 1% (w/v) SDS, 5% 2-mercaptoethanol and 20% glycerol, was applied to the top of a 4–40% continuous gradient polyacrylamide gel in a 10 μl capillary tube, as described by Rüchel et al. (16). Electrophoresis was carried out at 60 V for 60 min in 50 mM tris-glycine buffer (pH 8.4) in 0.1% SDS. The apparent molecular weights of the glycoproteins detected on the densitometric scan was estimated from the relative position of myosin, β-galactosidase, phosphorylase b, albumin, ovalbumin, carbonic anhydrase, trypsin inhibitor and α-lactalbumin, which were used as molecular weight markers. Gels were stained either with 0.2% Coomassie Brilliant Blue R-250 for protein or with periodic-Schiff’s reagent (PAS) for glycoprotein, and destained in 7% acetic acid. Gels were scanned with a Joyce-Loebl 3CS microdensitometer at a wave length of 595 nm for gels stained with Coomassie Blue and at 550 nm for those stained with PAS.

Drugs: Drugs used were dopamine hydrochloride (Sigma), haloperidol (Dainippon Pharmaceutical), phentolamine mesylate (Ciba-Geigy), propranolol hydrochloride (ICI Pharmaceutical) and atropine sulphate (Merck). The injection volume used in the present study was 0.1 ml/100 g body weight.

Statistical analysis: Data are presented as the mean±S.E. of data from 6 rats, in most cases. The statistical significance of differences was assessed by Student’s t-test.

Results

Secretory response of submandibular saliva: The maximum flow rate of submandibular saliva, following intraperitoneal injection of dopamine, was achieved 15–20 min after administration of a dose of 5 mg/kg, 10–15 min after a dose of 10 mg/kg and 5–10 min after doses of both 20 and 40 mg/kg, and the rate decreased gradually thereafter (Fig. 1A). The total volume
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Fig. 1. Effects of different doses of dopamine administered i.p. on the flow rate (A) and the total volume (B) of saliva elicited from the submandibular gland. Total volume is represented as μl of saliva secreted per 100 mg wet weight of the submandibular gland for 30 min after i.p. administration of dopamine. Each point represents the mean±S.E. of results from six animals.

secreted from the submandibular glands during the 30 min after administration of dopamine increased in a dose-dependent manner (Fig. 1B). Although the salivary flow rates induced by dopamine at doses of 10 or 40 mg/kg were reduced significantly by pretreatment with phentolamine, propranolol and haloperidol at any time after administration of dopamine, the inhibitory effects differed at different doses of dopamine. The order of inhibitory potency was propranolol>phentolamine>haloperidol at a low dose of dopamine (10 mg/kg) (Fig. 2A), and it was phentolamine>haloperidol>propranolol at a higher dose of dopamine (40 mg/kg) (Fig. 2B). When the dose of dopamine was 10 mg/kg, pretreatment with 1 mg/kg of phentolamine, haloperidol or propranolol decreased the flow rate by 78.9, 53.3 or 96.7%, respectively. At a dose of 2 mg/kg of blockers, the flow rate decreased by 87.5, 86.7 and 97.4% of that induced by dopamine without blocker, for the three inhibitors respectively. However, pretreatment with atropine at a dose of 1 or 2 mg/kg, prior to administration of dopamine at doses of 10 or 40 mg/kg, did not cause any significant inhibition of the secretory response (Fig. 2A, B).

Concentration of protein and total amounts of protein in saliva secreted from submandibular glands: The concentration of protein and the total amounts of protein in saliva secreted from the submandibular glands during the 30 min period after administration of dopamine increased progressively with increasing doses of dopamine (Table 1A). When the rats were pretreated with any one of the four blockers at doses of 1 and 2 mg/kg (i.v.) 30 min prior to administration of dopamine at doses of 10 and 40 mg/kg (i.p.), the concentration and total amounts of protein in submandibular saliva changed as shown in Table 1B. The concentration of protein in saliva evoked by 10 mg/kg of dopamine after pretreatment with 1 and 2 mg/kg of haloperidol or phentolamine did not change significantly, although these values increased when the dose of dopamine was 40 mg/kg. Pretreatment with 1 and 2
Fig. 2. Effects of pretreatment with various blocking agents on flow rate of submandibular saliva induced by dopamine at a dose of 10 mg/kg (A) and 40 mg/kg (B). Each blocking agent at a dose of 1 mg/kg (○—○) and 2 mg/kg (●—●) was injected i.v. 30 min prior to i.p. administration of dopamine (▲——▲). Each point represents the mean±S.E. of results for six animals.
Table 1. Effects of different doses of dopamine (A) and pretreatment with various blocking agents (B) on the concentration and total amounts of protein in saliva elicited from submandibular gland

### A

| Dose (mg/kg) | Protein conc. (mg/ml) | Total amount of protein (μg/100 mg wet wt./30 min) |
|--------------|-----------------------|--------------------------------------------------|
| 5            | 20.91±3.17 (5)        | 135.1±57.0 (5)                                   |
| 10           | 24.16±0.99 (6)        | 661.7±57.8 (6)                                   |
| 20           | 24.20±1.48 (6)        | 1228.5±80.2 (6)                                  |
| 40           | 27.63±1.87 (6)        | 1637.7±68.3 (6)                                  |

Each value represents the mean±S.E. Numbers in parentheses indicate the number of animals. Note that pretreatment with propranolol at 1 mg/kg, prior to administration of dopamine at a dose of 10 mg/kg, could not be estimated because of the small volume of evoked saliva. * and *** indicate a significant difference from the results with dopamine at a dose of 10 and 40 mg/kg at P<0.05 and P<0.001, respectively.

### B

| Blocker      | Dose (mg/kg) | Protein conc. (mg/ml) | Total amount of protein (μg/100 mg wet wt./30 min) | Protein conc. (mg/ml) | Total amount of protein (μg/100 mg wet wt./30 min) |
|--------------|--------------|-----------------------|--------------------------------------------------|-----------------------|--------------------------------------------------|
|              |              |                       |                                                  |                       |                                                  |
|              |              | 24.16±0.99 (6)        | 661.7±57.8 (6)                                   | 27.63±1.87 (6)        | 1637.7±68.3 (6)                                   |
| Haloperidol  | 1            | 28.19±1.69 (6)        | 355.8±24.2 (6)***                                | 42.66±2.62 (6)***     | 1553.9±64.3 (6)                                   |
|              | 2            | 19.60±1.43 (5)        | 90.7±16.0 (5)***                                 | 34.70±2.57 (6)*       | 1026.3±52.5 (6)***                               |
| Phentolamine | 1            | 27.77±4.59 (6)        | 175.8±43.0 (6)***                                | 45.68±1.57 (6)***     | 1108.7±49.4 (6)***                               |
|              | 2            | 25.66±3.56 (5)        | 108.2±25.5 (5)***                                | 44.13±1.83 (6)***     | 737.9±40.2 (6)***                                |
| Propranolol  | 1            | – (0)                 | – (0)                                             | 17.11±4.29 (6)*       | 631.8±172.4 (6)***                              |
|              | 2            | 4.36 (1)              | 9.0 (1)                                           | 4.89±0.81 (6)***      | 121.2±19.6 (6)***                                |
| Atropine     | 1            | 22.42±1.42 (6)        | 639.5±62.4 (6)                                   | 29.69±2.35 (6)        | 1628.0±44.2 (6)                                  |
|              | 2            | 23.37±1.88 (6)        | 593.4±70.9 (6)                                   | 29.79±2.92 (6)        | 1395.7±154.7 (6)                                 |

Each value represents the mean±S.E. Numbers in parentheses indicate the number of animals. Note that pretreatment with propranolol at 1 mg/kg, prior to administration of dopamine at a dose of 10 mg/kg, could not be estimated because of the small volume of evoked saliva. * and *** indicate a significant difference from the results with dopamine at a dose of 10 and 40 mg/kg at P<0.05 and P<0.001, respectively.
mg/kg of propranolol, however, decreased the concentration of protein to 18% of the control value. On the other hand, total amounts of protein in saliva were decreased by pretreatment with these three blocking agents, and the order of potency for inhibi-

Fig. 3. Typical densitometric scans of glycoproteins from submandibular functional segments and saliva, stained with PAS. A: (a) acini and (b) convoluted granular tubules isolated from a normal rat. B: submandibular saliva secreted after administration of dopamine at a dose of 40 mg/kg (a) and pretreatment with haloperidol (b), phentolamine (c) or propranolol (d) at doses of 2 mg/kg prior to administration of dopamine at a dose of 40 mg/kg. Each blocking agent was injected i.v. 30 min prior to i.p. administration of dopamine. Each sample of segments and saliva was applied to the gel at a 0.5 and 0.25 μg as protein, respectively. Electrophoresis was performed as described in Materials and Methods.
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Dopamine effects on rat submandibular gland were propranolol > phentolamine > haloperidol. By contrast, at a dose of 40 mg/kg of dopamine, with pretreatment by haloperidol, phentolamine, or propranolol at the dose of 1 mg/kg, the concentration of protein in the saliva increased by 1.54-, 1.65-, and 1.61-times, respectively; and pretreatment with 2 mg/kg of each blocker increased the protein concentration by 1.26-, 1.60-, and 5.65-times, respectively. Total amounts of protein in the saliva secreted from the submandibular gland were decreased by pretreatment with the above three blocking agents, and the order of potency for inhibition was propranolol > phentolamine > haloperidol. However, pretreatment with atropine at doses of 1 and 2 mg/kg, prior to administration of dopamine at doses of 10 or 40 mg/kg, changed neither the concentration nor the total amounts of protein secreted.

Electrophoretic profiles of the glycoproteins: The typical densitometric scans of the PAS-stained glycoproteins from secretory segments isolated from the submandibular gland of the normal rat showed that the acinar segments contain one major band, band I, and three minor bands, bands II, III, and IV, whereas the convoluted granular tubules segments contain one major band, band III, and two minor bands, band I and band II (Fig. 3). Molecular weights of the glycoproteins in bands I, II, III, and IV were 130 KDa, 44 KDa, 31 KDa, and 21.5 KDa, respectively; these values were calculated from a standard curve established with the mobilities of the marker proteins. Both the electrophoretic patterns and the molecular weight of each band obtained in this experiment coincide with our previously reported results (10).

The electrophoretic patterns of glycoproteins in submandibular saliva elicited by 40 mg/kg of dopamine (i.p.), alone or in combination with 2 mg/kg of various blocking agents (i.v.) are shown in Fig. 3. The glycoprotein profiles in submandibular saliva elicited by dopamine at a dose of 40 mg/kg showed one prominent band, band I, of higher intensity and two minor bands, III and IV. The profiles obtained at other doses of dopamine (5, 10, and 20 mg/kg) were similar to that obtained at a dose of 40 mg/kg. Bands I, III, and IV in dopamine-induced saliva were found to be electrophoretically indistinguishable from bands I, III, and IV of untreated segments of salivary glands, respectively. After pretreatment with haloperidol or phentolamine, however, dopamine at a dose of 10 mg/kg elicited no obvious change, and dopamine at a dose of 40 mg/kg increased the intensity of band I which is characteristic of the acinar segments. Thus the latter effect was more marked after pretreatment with 2 mg/kg than with 1 mg/kg. However, when propranolol was administered prior to dopamine at the dose of 40 mg/kg, the relative amount of band III increased to the relative proportion characteristic of convoluted granular tubule segments, and the intensity of band I decreased. Pretreatment with atropine prior to administration of dopamine at doses of 10 and 40 mg/kg caused no obvious changes (data not shown).

Discussion

Dopamine elicits a marked increase in the salivation of experimental animals, as previously reported for the submandibular gland of rats (9, 17) and the parotid gland of rats (9) and rabbits (18). Its potency, which we measured in vivo, is similar to that of α-adrenergic agents (14) and it is considerably more potent than β-adrenergic agents (11). When haloperidol, phentolamine and propranolol are administered at doses of 1 and 2 mg/kg (i.v.), 30 min before i.p. administration of dopamine at a dose of 10 or 40 mg/kg, the order of potency for inhibition of each blocking agent was altered by the dose level of dopamine, as shown in this paper. The greatest blocking of the effects of 10 mg/kg of dopamine was seen with propranolol, whereas at 40 mg/kg of dopamine, the greatest effect was obtained with phentolamine. Such findings suggest that dopamine, at low doses, mainly stimulates β-adrenoceptors, and at high doses, mainly acts on α-adrenoceptors. Since haloperidol has been demonstrated to attenuate dopamine-induced renal, mesenteric (19) and coronary (20) vasodilation in the dog, in a manner which is not affected by α- or β-adrenergic antagonists, haloperidol is
generally considered to be a specific blocking agent for the receptors of dopamine (21). Moreover, it has been reported that salivation of rabbit parotid glands induced by dopamine is inhibited almost completely by pretreatment with haloperidol, but not by pretreatment with α- and β-adrenergic antagonists (18).

On the other hand, release of amylase from slices of guinea-pig submandibular gland, induced by dopamine, has been reported to be partially inhibited by administration of haloperidol (22) and also by administration of α- and β-adrenergic antagonists (22). In our studies and those by other workers (9, 17) on salivation by the submandibular gland in rats, haloperidol did not completely block the salivation induced by dopamine. According to Yeh et al. (19), when haloperidol was injected into an artery approximately 30 sec prior to administration of dopamine, it was possible to demonstrate the attenuation of renal vasodilation. We have shown that the simultaneous administration of haloperidol (1 and 2 mg/kg, i.v.) and dopamine (10 and 40 mg/kg, i.p.) failed to block completely the secretion of saliva, although the blocking effects were slightly larger than those seen after administration of haloperidol 30 min prior to that of dopamine (data not shown).

In regard to the concentration of protein in saliva, administration of phentolamine or haloperidol prior to that of dopamine at a dose of 10 mg/kg exerted no obvious effects, but the concentration was increased significantly at a dose of 40 mg/kg of dopamine. By contrast, after pretreatment with propranolol prior to administration of either dose of dopamine, the concentration of protein in saliva decreased significantly, although the magnitude of the decrease was larger at a dose of 10 mg/kg of dopamine than at a dose of 40 mg/kg. It is well known that activation of β-adrenoceptors causes the secretion of a small volume of saliva rich in protein (23–25) and mucin (25, 26). Therefore, the increase in the concentration of protein in saliva induced by administration of phentolamine prior to that of dopamine at a dose of 40 mg/kg may be due to secretion of saliva which is mediated by the β-adrenoceptor, as a result of a blockade of the α-adrenoceptors. In contrast, the decrease of the concentration of protein, in the case of pretreatment with propranolol, may be due to secretion of saliva in response to stimulation of α-adrenoceptors and blockade of β-adrenoceptors. Janssen (27) and Yeh et al. (19) demonstrated that haloperidol exerts α-adrenergic blocking activity, because this agent reduced the renal vasoconstriction produced by dopamine at high doses and also reduced that by norepinephrine. Thus, it appears that the increase in the concentration of protein in saliva, induced by pretreatment with haloperidol, may be due to blockade of α-adrenoceptors rather than blockade of specific receptors for dopamine. However, when haloperidol is administered prior to doses of 10 and 40 mg/kg of dopamine, it causes blocking effects which are somewhat less potent than those of phentolamine. It seems likely, therefore, that the action of dopamine in the functional segments of rat submandibular gland may be different for small and large doses of dopamine. This possibility was investigated by analysis of the glycoproteins in saliva and functional segments of the submandibular gland.

After pretreatment with haloperidol or phentolamine, dopamine at doses of 10 and 40 mg/kg elicits the secretion of the band I glycoprotein, which is secreted characteristically in response to β-adrenergic agonists. After such pretreatment, the intensity of band I, characteristic of acini, was significantly increased by a dose of 40 mg/kg of dopamine, but not a dose of 10 mg/kg. These findings suggest that dopamine at a dose of 10 mg/kg acts on acinar cells and elicits the secretion of the glycoprotein which is characteristic of such cells. However, the intensity of band I was increased by administration of dopamine at a dose of 40 mg/kg. This increase may be due to a relative increase of acinar secretory components in saliva caused by blockade of the α-adrenoceptors in convoluted granular tubules, since the glycoprotein which is characteristic of convoluted granular tubule cells is secreted into saliva upon stimulation of α-adrenoceptors (11, 13). This result was confirmed by pretreatment with a β-adrenergic antagonist. After pretreatment with propranolol, dopamine at a dose of 40 mg/kg produced a significant increase in the in-
tensity of band I and an apparent increase in that of III, but the relative amount of band III was considerably lower than that previously found after i.p. administration of methoxamine at a dose of 8 mg/kg (11, 13). These observations indicate that dopamine at a dose of 40 mg/kg acts on both acinar cells and those of the convoluted granular tubules. In an electrophoretic study of the submandibular saliva of the rat, Abe and Dawes showed that i.p. administration of dopamine, at a dose of 40 mg/kg or lower, elicits the secretion of proteins characteristic of a response to β-adrenergic agonists. In the present study, however, i.p. administration of dopamine at a dose of 40 mg/kg elicited secretion of a glycoprotein characteristic of the response to α-adrenergic agonists in addition to β-adrenergic agonists. A partial blockade of β-adrenoceptors in acinar cells may result from i.v. administration of propranolol at a dose of 2 mg/kg.

These results, therefore, suggest that dopamine, in small doses, acts on acinar cells, whereas in large doses, it acts on both the cells of the convoluted granular tubules and those of the acini.

Acknowledgments: This study was supported in part by a Grant-in-Aid for Scientific Research (No. 60480404) from the Ministry of Education, Science and Culture of Japan.

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