Effects of Metaraminol on the Secretion of Fluid and Glycoproteins from the Rat Submandibular Gland

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Abstract—The actions of metaraminol on the secretion of fluid and glycoproteins from rat submandibular glands were investigated using phentolamine, propranolol and reserpine. Metaraminol at doses from 1 to 8 mg/kg (i.p.) increased the salivation and the amounts of protein in submandibular saliva in a dose-dependent manner. The salivation induced by metaraminol at 2 mg/kg was inhibited strongly by pretreatment with propranolol, whereas the salivation induced by metaraminol at 8 mg/kg was inhibited strongly by phentolamine. Reserpine inhibited the secretion of fluid caused by both doses of metaraminol. The electrophoretic profiles of saliva evoked by metaraminol at 2 mg/kg revealed two main bands of glycoprotein, I and IV, which originated from the acinus, and the intensities of these bands were decreased by treatment with propranolol, whereas the major band in saliva induced by 8 mg/kg of metaraminol was glycoprotein III, which originated from the granular tubules. The intensity of band III was decreased by pretreatment with phentolamine. These results suggest that metaraminol, at small doses, stimulates mainly the /3-adrenoceptor in the acinus, whereas at large doses, it prominently stimulates the a-adrenoceptors in the granular tubules, although metaraminol at small and large doses is able to stimulate a- and /3-adrenoceptors in rat submandibular gland.

Metaraminol, lev-o-1-(m-hydroxyphenyl)-2-amino-1-propanol, has been used clinically as a pressor agent for treatment of certain hypotensive states since its hemodynamic effect on humans was demonstrated by Madonla et al. (1). The drug is much less potent, but has longer duration of action than Neosynephrine, 1-epinephrine and norepinephrine (1). Much evidence gained from studies on the hearts of rats (2), mice (3), guinea pigs (4) and dogs (5) has shown that metaraminol is a potent releaser and depletor of norepinephrine in sympathetic nerve endings. Such an effect of the drug has also been demonstrated in the spleen, lung, liver, kidney and adrenals of rat (6). However, the action of metaraminol on the submandibular gland has not yet been clarified.

We reported previously that the species of glycoproteins contained in the rat submandibular gland differ markedly between the acini and the granular convoluted tubules (7), and that the species of glycoproteins characteristic of the acini are secreted into saliva in response to /3-adrenergic agents (8), whereas glycoproteins characteristic of granular convoluted tubules are mainly secreted in response to a-adrenergic agents (9-11).

The present study was carried out to elucidate the action of metaraminol on the rat submandibular gland by comparing the electrophoretic profiles of the glycoproteins contained in functional segments of the gland with those of saliva elicited by metaraminol alone or in combination with reserpine and a- or /3-adrenergic blocking agents.

Materials and Methods
Collection of submandibular saliva: Male Sprague-Dawley rats, ten weeks of age, were starved 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 separation 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 injection of metaraminol at doses of 1, 2, 4 and 8 mg/kg. Reserpine at a dose of 5 mg/kg was injected intraperitoneally 24 hr prior to the administration of metaraminol at doses of 2 and 8 mg/kg. Phentolamine at doses of 0.01, 0.1 and 1.0 mg/kg, propranolol at a dose of 1 mg/kg or both phentolamine and propranolol at a dose of 1 mg/kg was injected intravenously 30 min prior to the injection of metaraminol at doses of 2 or 8 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 weighed, and then 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 (7). Rats were anesthetized with pentobarbital (50 mg/kg, i.p.), and the submandibular gland was perfused via the carotid artery with a solution of collagenase which consisted of 0.1% collagenase (Sigma, Type II), 1.0 mM CaCl, 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 perfused via the carotid artery 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 fresh solution of collagenase, in an atmosphere of 95% O2 and 5% CO2. The slices were rinsed with ice-cold modified Hanks’ solution to remove collagenase. Each segment of the acini and granular convoluted tubules was micro-dissected out with needles under a stereo-microscope, and each dissociated segment was collected in a siliconized capillary tube (Drummond Microcaps, 50 µl).

SDS-polyacrylamide micro-disc electrophoresis: Each segment of the acinus and granular tubules was dissolved in an equal volume of a 6% (w/v) solution of sodium dodecyl sulphate (SDS), which contained 10% 2-mercaptoethanol and was heated at 90°C for 3 min. The protein content of each of the samples was determined by the method of Lowry et al. (12) with bovine serum albumin as the standard. One microliter 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 disc gel, in a 10 µl capillary tube, as described by Rüchel et al. (13). Electrophoresis was performed at room temperature 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 were estimated from the relative positions of myosin, β-galactosidase, phosphorylase b, albumin, ovalbumin, carbonic anhydrase, trypsin inhibitor and α-lactalbumin, which were used as standardized 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. The patterns of glycoproteins and proteins on the gels were recorded by photograph and spectrophotometric traces of the gels made with a Joyce-Loeble 3CS microdensitometer at a wavelength of 595 nm for gels stained with Coomassie Blue and at 550 nm for those stained with PAS.

Drugs: Drugs used were metaraminol bitartrate (Banyu Pharmaceutical), Reserpine (Sigma), Phentolamine mesylate (Ciba-Geigy), Propranolol hydrochloride (ICI Pharmaceutical). Other chemicals used were of commercially available reagent grade. Reserpine was dissolved in alcohol-acetic acid-water (20:1:1), at a concentration of 10 mg in 0.14 ml; appropriate dilutions of this solution with water were used for injections. 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 8 rats. The statistical significance of differences was assessed by Student’s t-test.

Results

Secretory response of submandibular glands: In control rats, the flow rate of saliva from submandibular glands increased gradually until 30 min after administration of metaraminol at a dose of 1 mg/kg, but the maximum flow rate was obtained during 20–25 min after administration of 2 mg/kg, and during 10–15 min after administration of 4 and 8 mg/kg of the drug (Fig. 1A). The total volume of saliva secreted during the course of 30 min from the submandibular glands of non-pretreated rats in response to metaraminol increased in a dose-dependent manner (Fig. 1B).

When phentolamine, propranolol or both phentolamine and propranolol were administered prior to metaraminol at doses of 2 or 8 mg/kg, the flow rate of saliva was lower than that of the control rats at any time of observation. When the dose of metaraminol was 2 mg/kg, pretreatment with phentolamine at doses of 0.01, 0.1 and 1.0 mg/kg decreased the total volume to 61.8, 32.6 or 19.5%, respectively, whereas pretreatment with propranolol at a dose of 1 mg/kg decreased the total volume to 18.7%. Pretreatment with both phentolamine (1 mg/kg) and propranolol (1 mg/kg) decreased the total volume to 3.5%. However, when the dose of metaraminol was 8 mg/kg, pretreatment with phentolamine at doses of 0.01, 0.1 and 1.0 mg/kg decreased the total volume to 58.4, 29.0 and 14.0%, respectively, whereas pretreatment with propranolol at a dose of 1 mg/kg decreased the total volume to 57.1%. Pretreatment with both phentolamine (1 mg/kg) and propranolol (1 mg/kg) decreased the total volume to 2.4% (Fig. 2).

When rats were pretreated with reserpine at a dose of 5 mg/kg, the total volume of saliva secreted after administration of metaraminol at doses of 2 and 8 mg/kg decreased to 28.0 and 78.8%, respectively, as compared with the volume of rats without reserpine (Fig. 3).

The concentration and total amounts of protein in saliva secreted from submandibular

![Fig. 1](image-url)

**Fig. 1.** Effects of different doses of metaraminol administered i.p. on the flow rate (A) and total volume (B) of saliva secreted from the submandibular gland. Total volume is represented as ml of saliva secreted per 100 mg wet weight of the submandibular gland for 30 min after i.p. administration of metaraminol. Each point represents the mean±S.E. of results from eight animals.
glands: In saliva secreted from the submandibular glands during 30-min after administration of metaraminol at doses of 1 to 8 mg/kg, the concentration of protein did not show any significant differences at the doses used, whereas the total amounts of protein increased progressively with increasing doses of metaraminol (Table 1).

When the rats were pretreated with phentolamine, propranolol or both phentolamine and propranolol at 30 min prior to administration of metaraminol at a dose of 2 or 8 mg/kg, the effects of metaraminol on the concentration and total amounts of protein in submandibular saliva changed as shown in Table 2. The concentration of protein in saliva evoked by 2 mg/kg of metaraminol increased when the dose of phentolamine was 1.0 mg/kg, but did not increase at phentolamine doses of 0.01 and 0.1 mg/kg. However, when the dose of metaraminol was 8.0 mg/kg, the concentration of protein was increased by the pretreatment with phentolamine at doses of 0.1 and 1.0 mg/kg. In contrast, the concentra-

![Fig. 2. Effects of phentolamine (PHT) and propranolol (PPR) on the secretion of submandibular saliva induced by metaraminol (MET). Each blocking agent was injected i.v. 30 min prior to i.p. administration of metaraminol at doses of 2 and 8 mg/kg. Each column represents the mean±S.E. of results from eight animals. * and *** indicate a significant difference from the results with control rats (metaraminol alone) at P<0.05 and P<0.001, respectively.](image)

![Fig. 3. Effects of reserpine on the secretion of submandibular saliva induced by metaraminol at doses of 2 and 8 mg/kg. Control group; 888 reserpine-pretreated group. Reserpine (5.0 mg/kg, i.p.) was given 24 hr before the administration of metaraminol. Each column denotes the mean±S.E. of results from 8 rats. *** indicates a significant difference from the results with control rats (metaraminol alone) at P<0.001.](image)

| Dose | Protein concentration (mg/ml) | Total amounts of protein (µg/100 mg wet wt./30 min) |
|------|-------------------------------|-----------------------------------------------|
| 1    | 12.92 ± 0.96 (5)              | 71.1 ± 13.2 (5)                               |
| 2    | 14.32 ± 0.66 (8)              | 417.3 ± 58.4 (6)                              |
| 4    | 15.29 ± 0.95 (8)              | 977.0 ± 165.3 (8)                             |
| 8    | 14.41 ± 1.15 (8)              | 1305.9 ± 130.5 (8)                            |

Each value represents the mean±S.E. of results; numbers in parentheses indicate the number of animals from which results were obtained in each case.

Table 1. The concentration and total amounts of protein in saliva elicited from submandibular glands in response to metaraminol at different doses.
Table 2. Effects of pretreatment with adrenergic blocking agents or reserpine on the concentration and total amounts of protein in saliva elicited from submandibular glands in response to metaraminol

| Drugs       | Dose (mg/kg) | Metaraminol (2 mg/kg) | Metaraminol (8 mg/kg) |
|-------------|--------------|-----------------------|-----------------------|
|             |              | Protein concentration (mg/ml) | Total amounts of protein (µg/100 mg wet wt./30 min) | Protein concentration (mg/ml) | Total amounts of protein (µg/100 mg wet wt./30 min) |
| Control     | —            | 14.32±0.66 (8)        | 417.3±58.4 (8)        | 14.41±1.15 (8)              | 1305.9±130.5 (8)          |
| Phentolamine| 0.01         | 16.32±0.67 (8)        | 259.2±39.1* (8)       | 17.48±1.42 (8)              | 901.8±122.6* (8)          |
|             | 0.1          | 16.19±1.43 (7)        | 153.7±27.0** (7)      | 20.87±1.65* (8)             | 551.1±34.7*** (8)         |
|             | 1            | 22.75±1.35*** (5)     | 118.4±10.2** (5)      | 24.11±1.00*** (8)           | 325.0±25.4*** (8)         |
| Propranolol | 1            | 3.12±0.46*** (5)      | 19.0±3.4*** (5)       | 6.56±0.96*** (8)            | 341.4±50.0*** (8)         |
| Phentolamine+Propranolol | 1 | 6.28±0.32*** (5) | 7.4±0.3*** (5) | 6.94±0.44*** (7) | 17.5±3.2*** (7) |
| Reserpine   | 5            | 29.55±2.00*** (6)     | 224.9±51.0 (6)        | 19.80±2.41 (8)              | 1319.3±122.4 (8)          |

Phentolamine, propranolol or both phentolamine and propranolol was injected i.v. 30 min prior to i.p. administration of metaraminol. Reserpine (5.0 mg/kg, i.p.) was given 24 hr before the administration of metaraminol. Each value represents the mean±S.E. of results; numbers in parentheses indicate the number of animals from which results were obtained in each case. *, ** and *** indicate a significant difference from the results with metaraminol alone at P<0.05, P<0.01 and P<0.001, respectively.
tration of protein in saliva evoked by metaraminol at doses of 2 and 8 mg/kg was decreased by pretreatment with propranolol at a dose of 1 mg/kg or both phentolamine and propranolol (1 mg/kg), but these values were considerably lower than those obtained after pretreatment with phentolamine at a dose of 1 mg/kg. When metaraminol was administered at a dose of 2 mg/kg, the amounts of protein in saliva decreased to 62.1, 36.8 and 28.4% after pretreatment with phentolamine at doses of 0.01, 0.1 and 1.0 mg/kg, respectively; and the amount decreased to 4.6% after pretreatment with propranolol at a dose of 1.0 mg/kg. Furthermore, when metaraminol was administered at a dose of 8 mg/kg, the amounts of protein decreased to 69.1, 42.2 and 24.9% after pretreatment with phentolamine at doses of 0.01, 0.1 and 1.0 mg/kg, respectively; and the amount decreased to 26.2% after pretreatment with propranolol at a dose of 1 mg/kg. When the rats were pretreated with both phentolamine (1 mg/kg) and propranolol (1 mg/kg), the amounts of protein in saliva evoked by metaraminol at doses of 2 and 8 mg/kg were decreased to 1.8 and 1.3%, respectively (Table 2).

When rats were pretreated with reserpine at a dose of 5 mg/kg, the concentration of protein in saliva evoked by metaraminol at doses of 2 or 8 mg/kg increased 2.06-fold and 1.37-fold, compared to values obtained with metaraminol alone, respectively, but the total amount of protein in saliva decreased to 58.7% after metaraminol at the dose of 2 mg/kg, while it did not change after the 8 mg/kg dose (Table 2).

Electrophoretic profiles of the glycoproteins in secretory segments and saliva: Typical densitometric scans of the glycoproteins from the submandibular glands of normal rats showed that the acinar segments contain one major band, band I, and three minor bands, bands II, III and IV, whereas the granular convoluted tubules segments contain one major band, band III, and two minor bands, bands I and II (data not shown). Glycoprotein bands in saliva evoked from submandibular glands by metaraminol consisted of bands I, III and IV. Bands I, III and IV in this saliva were found to be electrophoretically identical to bands I, III and IV of the secretory segments of the submandibular gland, respectively; and the apparent molecular weights of the material in bands I, III and IV were 130 KDa, 31 KDa and 21.5 KDa, respectively. However, the relative intensities of these bands differed significantly following administration of metaraminol; at small doses of metaraminol, the intensity of bands was higher for bands I and IV than for band III, whereas at large doses, the intensity of band III was higher than that of bands I and IV. When phentolamine at doses of 0.01, 0.1 and 1.0 mg/kg or propranolol at a dose of 1.0 mg/kg was administered prior to metaraminol at doses of 2 and 8 mg/kg, the typical densitometric scans of the glycoproteins from submandibular saliva were altered, as shown in Fig. 4.

When the dose of metaraminol was 2 mg/kg, pretreatment with phentolamine at a dose of 1 mg/kg caused an increase in the intensity of band I, whereas pretreatment with propranolol at a dose of 1 mg/kg caused a significant decrease of the intensity of band I and a small increase in the intensity of band III. In contrast, with a dose of 8 mg/kg of metaraminol, pretreatment with phentolamine at doses of 0.1 and 1 mg/kg caused an increase in the intensity of band I and a decrease in band III, while phentolamine at a dose of 0.01 mg/kg did not change the profiles. When rats were pretreated with propranolol at a dose of 1 mg/kg, profiles of the glycoproteins were similar to those elicited by metaraminol at a dose of 8 mg/kg alone. Furthermore, when rats were pretreated with both phentolamine (1 mg/kg) and propranolol (1 mg/kg), metaraminol at a dose of 2 mg/kg caused decreases in the intensities of bands I and IV, whereas metaraminol at a dose of 8 mg/kg showed profiles similar to that after pretreatment with phentolamine at a dose of 1 mg/kg only (data not shown). When rats were pretreated with reserpine, the electrophoretic profiles of the glycoproteins from the submandibular saliva elicited by 2 or 8 mg/kg of metaraminol were similar to those in saliva elicited by metaraminol alone (data not shown).
Fig. 4. Effects of phentolamine (PHT) and propranolol (PPR) on densitometric profiles of glycoproteins in submandibular saliva secreted after administration of metaraminol. Each blocking agent was injected i.v. 30 min prior to i.p. administration of metaraminol at doses of 2 and 8 mg/kg. Salivary samples secreted during the 30 min after administration of metaraminol were applied to the gel at a concentration of 0.25 μg of protein per sample. Electrophoresis was performed as described in Materials and Methods.

Discussion

Metaraminol elicits the secretion of fluid (Fig. 1) and protein (Table 1A) from submandibular glands of rats in a dose-dependent manner. The volumes of fluid and the concentrations or amounts of protein in saliva secreted after administration of metaraminol
were similar to those with methoxamine reported previously (9-11). The submandibular gland of the rats consists of two secretory segments, the acini and granular tubules (14). In the present study, the electrophoretic profiles of secretory segments showed that the glycoprotein bands in the acinar segments consisted of one major band (I) and three minor bands (II, III and IV), whereas the granular tubule segments revealed one major band (III) and two minor bands (I and II), as shown by us previously (7). The profile of the glycoproteins elicited in saliva from the submandibular glands by a small dose of metaraminol revealed band I as the prominent band and band IV as a minor band, whereas at large doses of metaraminol, band III was prominent and band I was the minor band (Fig. 4). Therefore, it appears that metaraminol at a dose of 2 mg/kg mainly stimulates the \( \beta \)-adrenoceptors in acinar cells, since pretreatment with phentolamine did not produce a significant increase in the intensity of band III. In contrast, when the dose of the metaraminol was 8 mg/kg, pretreatment with phentolamine at a dose of 1 mg/kg caused a marked increase in the intensities of bands I and IV and a marked decrease in the intensity of band III, whereas pretreatment with propranolol at a dose of 1 mg/kg gave glycoprotein profiles similar to those seen with the control rats given metaraminol alone (Fig. 4). Therefore, these findings suggest that metaraminol at a dose of 8 mg/kg mainly stimulates \( \alpha \)-adrenoceptors in granular tubules. In this case, however, the \( \alpha \)-adrenoceptor appears to be of the \( \alpha_1 \) subtype, since the glycoproteins in granular tubules of rat submandibular gland are elicited via the stimulation of \( \alpha_1 \)-adrenoceptors rather than \( \alpha_2 \)-adrenoceptors (11). Thus, secretion of glycoproteins from granular tubules induced by metaraminol at large doses may be mainly attributable to activation of \( \alpha_1 \)-adrenoceptors.

In addition, the electrophoretic findings showed that the intensity of bands I and IV in saliva elicited by metaraminol at a dose of 2 mg/kg was markedly reduced by pretreatment with propranolol at a dose of 1 mg/kg, as shown in Fig. 4. These findings suggest that metaraminol at a dose of 2 mg/kg mainly stimulates the \( \beta \)-adrenoceptors in acinar cells, since pretreatment with phentolamine did not produce a significant increase in the intensity of band III. In contrast, when the dose of the metaraminol was 8 mg/kg, pretreatment with phentolamine at a dose of 1 mg/kg caused a marked increase in the intensities of bands I and IV and a marked decrease in the intensity of band III, whereas pretreatment with propranolol at a dose of 1 mg/kg gave glycoprotein profiles similar to those seen with the control rats given metaraminol alone (Fig. 4). Therefore, these findings suggest that metaraminol at a dose of 8 mg/kg mainly stimulates \( \alpha \)-adrenoceptors in granular tubules. In this case, however, the \( \alpha \)-adrenoceptor appears to be of the \( \alpha_1 \) subtype, since the glycoproteins in granular tubules of rat submandibular gland are elicited via the stimulation of \( \alpha_1 \)-adrenoceptors rather than \( \alpha_2 \)-adrenoceptors (11). Thus, secretion of glycoproteins from granular tubules induced by metaraminol at large doses may be mainly attributable to activation of \( \alpha_1 \)-adrenoceptors.

The direct and indirect actions of metaraminol at doses of 2 and 8 mg/kg on the secretion of fluid, protein and glycoproteins from the submandibular gland were examined in rats pretreated with reserpine. Reserpine was used at a dose of 5 mg/kg, which caused nearly maximal depletion of cardiac norepinephrine in the rat (5). The saliva evoked by administration of 2 mg/kg of metaraminol in reserpine-treated rats has significantly higher concentrations of protein (Table 2), but significantly smaller volumes (Fig. 3) as compared with the those in reserpine-untreated rats. In
this case, the secretion of saliva may be due mainly to stimulation of the postsynaptic β-
adrenoceptors, since the characteristics of saliva secreted by metaraminol at a dose of 2 mg/kg are similar to those elicited by β-adrenergic agents rather than α-adrenergic agents. Thus, the present data appears that metaraminol at a dose of 2 mg/kg may exert direct and indirect actions on the submandibular gland. However, in the case of metaraminol at a dose of 8 mg/kg, the effects of reserpine treatment on the concentrations of protein and total amounts of protein (Table 2) and flow rate (Fig. 3) of the saliva were considerably smaller than those of metaraminol at a dose of 2 mg/kg. It has been reported that reserpine did not reduce the immediate and transitory actions of metaraminol on blood pressure of the rat (5). This observation is consistent with the results of metaraminol at large doses in the present study. Anton and Berk (6) have reported that administration of metaraminol at doses of 1.3 and 5 mg/kg caused the depletion of norepinephrine in many organs of the rat. In the reserpine pretreated-rat, no significant changes in the protein concentration and electrophoretic profiles of glycoproteins are observed in the saliva elicited by administration of metaraminol at a dose of 8 mg/kg. A possible explanation for this is that the postsynaptic-adrenoceptors mediating the response to metaraminol at a dose of 8 mg/kg are of the α-type in the case of either indirect or direct actions. However, the indirect action of metaraminol at a dose of 8 mg/kg could not disregarded, since flow rates were reduced to some extent by pretreatment with reserpine. Therefore, it appears that metaraminol at doses of 2 and 8 mg/kg acts as a partial agonist on the rat submandibular glands, as generally recognized in other organs.

In conclusion, the present study showed that metaraminol, at small doses, mainly stimulates the β-adrenoceptors in the acini, whereas at large doses, it prominently stimulates the α-adrenoceptors in the granular tubules, although metaraminol at small and large doses is able to stimulate α- and β-adrenoceptors in the submandibular gland of the rat.

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