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Effect of the Chronic Administration of Isoproterenol on the Oxygen Uptake in Rat Submandibular Glands

Keiko Nakano

Summary

The oxygen uptake in rat submandibular glands treated with isoproterenol was measured by utilizing various agents. The chronic administration of isoproterenol (2.5 mg/100 g body weight/day s. c., for 6 days increased the weight of submandibular glands compared with that of the untreated control by 2.65-fold. Although the oxygen uptake in the treated tissue was increased by the addition of adrenaline, noradrenaline, phenylephrine of pilocarpine, the level of the oxygen uptake was considerably low compared with the case of the normal tissue. On the other hand, isoproterenol and substance P significantly increased the oxygen uptake in the normal tissue, but did not in the treated tisste. Adrenaline response in the normal tissue was inhibited by both phentolamine and propranolol, whereas that in the treated tissue was inhibited by phentolamine, but was not by propranolol. Pilocarpino response in the normal and treated tissue was inhibited by atropine. From these data it is concluded that the chronic administration of isoproterenol causes the change of α- and β-adrenergic, muscarinic and peptide receptors related to the oxygen uptake.

Intrduction

Since Selye et al. (7) reported that the chronic administration of a large dose of isoproterenol (IPR) caused enlargement of the salivary glands of rats, many morphological studies have been carried out (1, 8). The enlargement of the salivary glands caused by IPR is accompanied by the stimulant effect of DNA synthesis (2, 3). Durham (3) reported that IPR (0.3 mmole/kg body weight), when injected into the mouse interaperioneally, increased the weight by 35% and stimulated DNA synthesis 30-fold in the protid glands. Such morphological study has been carried out, but physiological and pharmacological study has not been carried out on the enlarged glands to clarify various aspectes of the cellular hypertrophy.

The author studied the response of the oxygen uptake caused by various pharmacological agents in the enlarged submandibular glands by the chronic administration of IPR.

Materials and Methods

The rats used in this experiment were Wistar strain males weighing 180-200 g. The animals had free access to a standard pelleted diet and water, and were divided into 2 groups : the untreated control that received the sterile saline and the treated group that received the administration of IPR (2.5 mg/100 g body weight/day, s. c.) for 3 or 6 consecutive day. The animals were fasted for 18 hr prior to sacrifice and killed by a blow on the head. The submandibular glands were removed and placed in a Krebs-Ringer phosphate buffer (pH 7.4), and cut with Stadie-Riggs slicer into slices (slice thickness ca. 0.5-0.8 mm). Warburg vessels each containing a tisste of approximately 60-80 mg were immersed in 3 ml medium. The oxygen uptake was measured by Warburg's mononetric method under pure oxygen for 60 minutes at 37.5 °C The adition of reagents was made after preincubation for 10 minutes.

The drugs used were : adrenaline and noradrenaline from Sankyo Co., Pilocarpine and atropine from Sanko Co., IPR from Tokyo Kasei Co., Phenylephrine from Sigma Chemical Co., Propranolol from Sumitomo Kagaku Co., Substance P from protein Research Fundation, Japan.

Results

The administration of IPR for 3 days did not increase the weight of submandibular glands compared with that of the untreated control, but that of IPR for 6 days increased the weight by 2.65-fold.

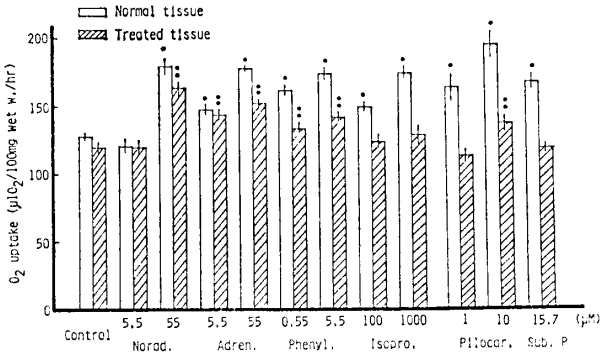

Fig. 1 Effect of pharmacological agents on the oxygen uptake in the normal and treated tissue.
*, ** $P<0.001$ compared with control value.
Each column represents mean ± SEN for seven experiments.

Figure 1 represents the change of the oxygen uptake caused by various agents in the tissue treated with IPR for 6 days and its control. The oxygen uptake in both the normal and treated tissue was increased by the addition of noradrenaline, adrenaline, phenylephrine or pilocarpine, compared with the control level. However, the level of the oxygen uptake which was observed in the treated tissue was significantly low compared with that of the normal tissue. On the other hand, the oxygen uptake of the normal tissue was apparently increased by the addition of IPR and substance P, but that of the treated tissue was not.

Table 1 demonstrates the effect of phentolamine, propranolol, and atropine on the adrenaline and pilocarpine response in both the normal and treated tissue. Phentolamine, an α-adrenergic blocking agent, significantly blocked the increase of the oxygen uptake by adrenaline in both the normal and treated tissue. On the other hand, a low concentration of propranolol (10 μM), a β-adrenargic blocking agent, did not inhibit the adrenaline response in the normal and treated tissue, and when the concentration of propranolol was increased to 33.8 μM, the adrenaline response in the normal tissue was significantly blocked, but that in the treated tissue was unaffected. And the oxygen uptake by pilocarpine in both the normal and treated tissue was apparently inhibited by the addition of atropine, a cholinergic blocking agent.

Conditions	O_2 uptake (μlO_2/100mg wet w./hr)	
	Normal tissue	Treated tissue
Control	139 ± 4	122 ± 5
55 μM Adrenaline	178 ± 3	152 ± 4
+10 μM Phentolamine	138 ± 4 *	123 ± 6 *
+100 μM Phentolamine	132 ± 5 *	129 ± 6 *
+10 μM Propranolol	181 ± 4 NS	149 ± 3 NS
+33.8 μM Propranolol	154 ± 3 *	145 ± 5 NS
10 μM Pilocarpine	196 ± 9	138 ± 6
+10 μM Atropine	129 ± 3 *	107 ± 4 *
+100 μM Atropine	127 ± 2 *	103 ± 3 *

Table 1 Effect of phentolamine, propranolol and atropine on the oxygen uptake caused by adrenalin and pilocarpine.
NS; Not significantly, * $P<0.001$ compared with the corresponding value with adranaline or pilocarpine.
Each value represents the mean± SEN for seven experiments.

Discussion

Previous studies have shown that pilocarpine, a cholinergic agonist, dose not increase the weight of salivary glands, but IPR, a β-adrenergic agonist, sgnificantly increases it (6). The enlargement of the glands in response to IPR is rapid and results from both cellular hypertrophy and hyperplasia (1, 8). Although Selye et al. (7) observed the enlarged submandibular glands caused by a large dose of IPR (37.3 mg/100 g body weight, daily twice) given for 17 days, the author demonstrated that the glands were enlarged by applying a low concentration

of IPR for a short duration. And the author have confirmed by histologic study that the size of the acinar cells in the enlarged glands was greatly increased compared with that of the control animal glands.

It is known that adrenergic and cholinergic agonists or substance P stimulate the metabolism of salivary glands (4, 5). In the present experiment, it was observed that a remakable increase in the oxygen uptake was produced by adrenergic and cholinergic agonists or substance P in the normal tissue. On the other hand, the oxygen uptake in the treated tissue was stimulated by the addition of adrenaline, noradrenaline, Phenylephrine or pilocarpine. However, the level of the oxygen uptake was considerably low compared with the case of the normal tissue. The stimulating effect of bote IPR and substance P was not observed effectively. The oxygen uptate caused by adrenaline in the normal tissue was inhibited significantly by phentolamine and propranolol. On the other hand, the oxygen uptake caused by adrenaline in the treated tissue was inhibited significantly by phentolamine, but was not propranolol. This finding suggests that the increase of the oxygen uptake in the treated tissue evoked by stimulated α-receptors in the cells. The oxygen uptake in the normal and treated tissue that was caused by the addition of pilocarpine was inhibited considerably atropine.

These results suggest that the chronic administration of IPR provokes the change of various receptors (α- and β-adrenergic, muscarinic, and peptide receptors) related to the oxygen uptake. However, more studies are necessary to clarify the change of receptors in the cell level.

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Refereces

1. K. Brown-Grant, Nature **191** 1076-1078 (1961).
2. T. Barka, Exptl. Cell Res. **39** 355-364 (1965).
3. J.P. Durham, Life Sci. **26** 1423-1430 (1980).
4. Z. y. Friedman and Z. Selinger, J. Physiol., London **278** 461-469 (1978).
5. T. Komabayashi, S. Sakamoto and M. Tsuboi, Jap. J. Pharmacol. **29** 707-713 (1979).
6. E. Nezu and H. Nakamura, J. Oral Biol. **19** 500-506 (1977).
7. H. Selye, R. Veilleux and M. Cantin, Science **133** 44-45 (1961).
8. C. A. Schneyer, Am. J. Physiol. **203** 232-236.

ラット顎下線の酸素摂取におよぼすイソプロテレノールの連続投与の影響

中野慶子

要　約

isoproterenol 処理を受けたラット顎下腺の酸素摂取におよぼす各種薬物の影響を検討した。isoproterenol (2.5 mg/100 g weight/day s. c., for 6 days) の連続投与によって顎下腺の重量は未処理のものに比べて 2.65 倍の増加を示した。処理組織における酸素摂取は Adrenaline, Noradrenaline, phenlephrine, および pilocarpin の添加によって増加したが，酸素摂取 level は未処理の組織の場合に比較して低かった。一方，isoproterenol および substance P は，未処理組織の酸素摂取を有意に増加させたが，isoproterenol 処理組織の酸素摂取に影響しなかった。未処理組織における adrenaline の効果は phentolamine および Propranolol の添加によって抑制された。しかしながら，処理を受けた組織では phentolamine によって抑制されたが propranolol では抑制されなかった。未処理組織および処理組織における pilocarpine の結果は atropine によって抑制された。これらの結果から isoproterenol の連続投与は酸素摂取と関連を持つ α- および βアドレナリン受容体，ムスカリン受容体ならびにペプタイド受容体の変化を惹起することが示唆された。