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Effects of adrenoceptor blockers on the glycemic response to nicotine in thyroidectomised rats

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Summary
The effect of adrenoceptor blockers on nicotine induced hyperglycemia were studied in fasted normal and thyroidectomised rats. Blood glucose was estimated using the modified glucose oxidase method. The control experiments consisted of sham operated rats with intact thyroid glands. Pre-treatment of the rats with either the alpha adrenoceptor blocker prazosin or the beta adrenoceptor blocker propranolol before intravenous injection of nicotine (50 μg/kg) significantly reduced the hyperglycemia induced by nicotine in normal rats, while a combination of propranolol and prazosin abolished nicotine induced hyperglycemia. In the thyroidectomised group, nicotine also caused hyperglycemia. However, the basal glucose level and peak of glycemic response were lowered compared to that in the control group. The results therefore seem to suggest that both alpha and beta adrenoceptors are involved in nicotine-induced hyperglycemia in the rat.

Keywords: *Adrenoceptor blockers, nicotine, thyroidectomised, hyperglycemia, sham operated*

Résumé
L'effect de blocquoueurs d' adrenorecepteurs sur l'hyperglycamic in duite par la nicotine avait ete etudies chez les rats nor maux et sans tyroide a feune. Le taux de glucose sanguin avait ete estime entuditant la methode modifie du glucose oxidare decrite par Trinder (1969). Les experiences de controles avaient consiste des rats the type sham avec des glandes tyroides intactes. Le pre-traitement des rats avec toit les blocqueurs alpha d'adrenorecepteurs prozasin on blocqueurs d'adrenorecepteurs B pro panol avaint l'infection intraveineure de nicotine (50mg/1kg) avait significativement l'hyperglicemie induite par la nicotine chez les rats normaux. La combination du propanolol et du prazosin avaiet inhibe lily perglyicemic induite par la nicotine. Chez les groupes de rats sans tyroide, la nicotine avait aussi cause l' hyperglicemie copendant, le taux de glucose de base et le peak dereponse glycemique avaient ete dumimue compare a ceux des animaux dans le groupe der controle. Ces resultats par consequent semble suggere que les adrenorecepteurs & et B sont implique l' hyperglicemie chez les rats.

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Introduction

Studies have shown that injection of nicotine into animals' results in a measurable and often marked increase in blood glucose. Such observations have been made in animals such as dogs [1,2,3] rabbit [4,5] and rats [6,7]. The mechanism by which nicotine induces hyperglycemia has been determined [8]. Larson *et al.* [9] showed that nicotine stimulates the release of adrenaline from the chromaffin granules in the adrenal glands. Indeed, Tsuijimoto *et al.* [10] reported abolition of the nicotine-induced hyperglycemia following adrenalectomy in the rat. Thus the mechanism by which nicotine increases blood glucose is through an indirect effect, that is, nicotine causes the release of adrenaline which induces hyperglycemia [6,10].

The receptors involved in nicotine-induced hyperglycemia unlike adrenaline and other sympathomimetic amines have not received much attention from research workers. However, there are reasons to believe that the receptors mediating nicotine-induced hyperglycemia are similar to those of adrenaline induced hyperglycemia. In a study conducted by Grayson and Oyebola [3] it was observed that Beta receptor blockade with propranolol significantly reduced the hyperglycemic response to nicotine infusion while alpha receptor blockade with prazosin abolished the large increases in arterial and venous glucose levels caused by nicotine in dogs. This led to the conclusion that the effect of nicotine on blood glucose in the dog is predominantly alpha-mediated.

A similar study on the involvement of adrenoceptors in nicotine hyperglycemia in the rat was conducted by Oyebola and Alada [7]. It was observed that in contrast to the case in the dog, propranolol abolished while prazosin only reduced nicotine-induced hyperglycemia in the rat. This provides an evidence that

the abolition of nicotine induced hyperglycemia may be species related since blood glucose levels were abolished in dogs by alpha blockade whereas it was by beta blockade in rats.

For several years, the permissive effect of thyroid hormones on adrenergic activity has been of interest to investigators. Indeed adrenaline and noradrenaline effects are potentiated by thyroid hormones in what is referred to as the upregulation [11, 12]. A classical example of such effect is observed in clinical presentations associated with hyperthyroidism [13] in which thyroid hormones potentiate the activities of adrenoceptors on the heart and other tissues [14,15]. It is however not clear if such a relationship exists between thyroid hormones and adrenoceptors on the metabolic activity of the body. The present study was therefore undertaken to investigate further, the role of adrenoceptors in nicotine-induced hyperglycemia and also the influence of thyroid hormones on the observed role.

Materials and methods

Male albino rats of the Wistar strain weighing between 180 and 200g were used for the experiments.

Thyroidectomy

Each animal was anaesthetized by intraperitoneal administration of sodium pentobarbitone at 30 mg/kg per body weight and this was followed intermittently with diethyl ether by inhalation through cotton wool as required in the course of the surgery. A single longitudinal skin incision anterio-ventrally was made on the neck of the rat. By cautious teasing of the overlying tissues, the thyroid gland was isolated and removed after ligation of the thyroid arteries. Some amount of procaine penicillin was then applied in the operated area to forestall infection and then the incision was sutured back. The animals were allowed to recover completely from surgery for about 10 weeks after which the nicotine experiments were carried out on them.

Experimental procedure

Each animal was fasted for 18 - 24 hours before the commencement of an experiment. The experiments were carried out on 8 groups of rats consisting of 8 rats per group. Rats in groups 1, 2, 3 and 4 were subjected to similar surgical procedure as mentioned above but their thyroid glands were not removed (sham operation). All the four groups received a bolus injection of nicotine, 50 ug/kg through the femoral vein, which was cannulated. However rats in groups 2, 3 and 4 were pretreated with prazosin, propranolol and a mixture of prazosin and propranolol respectively. Each pretreatment with the adrenoceptor blocker was done by an intravenous injection through the femoral vein and nicotine administered after 30 minutes.

For nicotine experiments, anesthesia was induced with 0.6 ml/100 g of 25 percent (w/v) urethane solution administered intraperitoneally. Rats in groups 5, 6, 7 and 8 were thyroidectomised and given bolus injection of nicotine 50 ug/kg intravenously. Groups 6, 7 and 8 rats were similarly pretreated with prazosin, propranolol and a combination of prazosin and propranolol respectively.

Blood sampling procedure

From the carotid artery which was cannulated in the course of the surgery, blood samples of 0.05 ml was drawn directly into a micropippete before nicotine injection and serial samples were taken at 10, 20, 60, 90 and 120 minutes post injection. The preparation of the animals and blood sampling for glucose estimation were as previously described [16].

Blood glucose estimation

Each sample of blood (0.05 ml) was immediately transferred into 2.95 ml of protein precipitant. Blood glucose concentration was measured using the glucose oxidase method of Trinder [17].

Statistical analysis

A t-test of difference between two sample means [18] or a paired t-test was used as appropriate as in [16]. P values of 0.05 or less were taken as statistically significant.

Results

Effects of nicotine on blood glucose level in normal and thyroidectomised rats

Figure 1 shows the effect of nicotine injections on blood glucose levels in normal and thyroidectomised rats. Nicotine in normal rats caused an immediate but gradual increase in blood glucose level, which reached its peak 60 minutes post injection, and thereafter there was a gradual drop in blood glucose levels. In thyroidectomised rats, there was a slight but significant reduction in the basal blood glucose level.

Effect of alpha and beta adrenoceptor blockers on nicotine-induced hyperglycemia in normal rat

This is shown in Figure 2. Prazosin significantly reduced nicotine-induced hyperglycemia but did not abolish the hyperglycemic response to nicotine injection, while pretreatment with propranolol alone as well as a combination of propranolol and prazosin

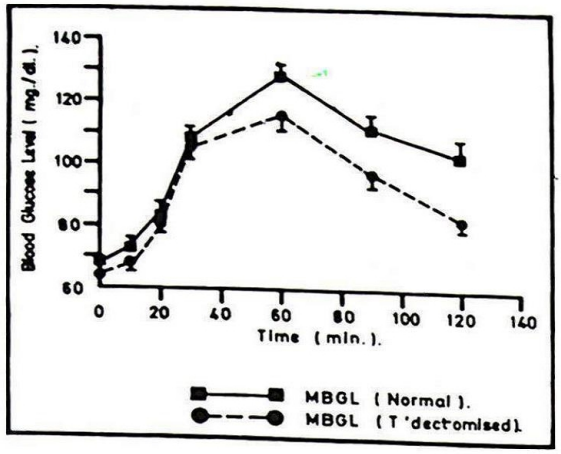

Fig. 1: Effects of nicotine (50μg I.V.) on blood glucose levels in normal (— • —) and thyroidectomised (—•—) rats. Note the marked hyperglycemia, which attained a peak 60 min. Post injection in the normal rats and significantly reduced level of peak hyperglycemia in thyroidectomised rats. $P < 0.05$

completely abolished the nicotine-induced hyperglycaemia.

Effect of alpha and beta adrenoceptor blockers on nicotine-induced hyperglycemia in thyroidectomised rats

Figure 3 shows the effect of prazosin and propranolol on glycemic response to nicotine injection in thyroidectomised rats. A combination of prazosin and propranolol completely abolished nicotine-induced hyperglycemia in thyroidectomised rats.

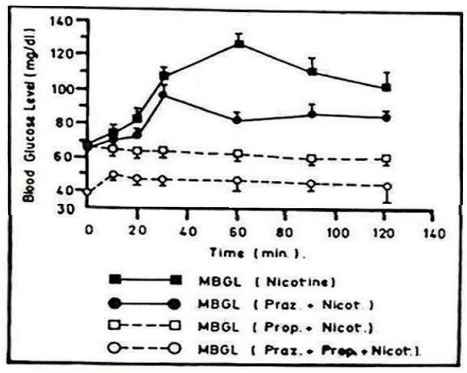

Fig. 2: Effect of Prazosin (0.2mg/kg i.v.) (—•—) and Propanolol (0.5mg i.v) (—□—) on glycemic response to nicotine (50 μg/kg) in normal rats. Note that prazosin and propranolol reduced the hyperglycemic effect of glucose when singly administered and completely abolished this effect when jointly administered (—o—)

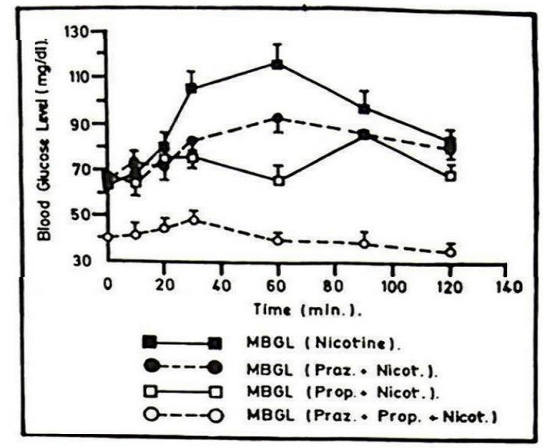

Fig.3: Effects of prazosin (0.2 mg/kg i.v.) (—•—) and propanolol (0.5mg i.v) (—□—)as well as a combination of Prazosin and Propranolol (0.2mg/kg i.v, 0.5mg i.v) respectively (—o—) on glycemic response to nicotine in thyroidectomised rats. Note the complete abolishing of nicotine induced hyperglycemia in this group.

Discussion

The observed hyperglycemia induced by nicotine in the rat in this study is consistent with its well-known pharmacological effects on blood glucose. Previous studies in the cats and dogs [10,3] showed that thehyperglycemia induced by nicotine is mainly due to the adrenaline released from the adrenal medulla. In this study pretreatment of the rat with alpha adrenoceptor blocking agent (prazosin) significantly reduced but did not abolish the large hyperglycemic response to nicotine injection. This result agrees with that of Oyebola and Alada [7]. It however contrasts with the findings of Grayson and Oyebola [3] who observed the abolition of the hyperglycemic response to nicotine infusion in dogs by prazosin. This difference is probably due to specie variation. Indeed different workers have demonstrated the existence of such species difference [22, 23].

The result in the present study also showed that propranolol abolished the large hyperglycemia induced by nicotine. This result is consistent with that of Oyebola and Alada [7] on the effect of propranolol on glycemic response to adrenaline.

The effect of nicotine on blood glucose in thyroidectomised rats in this study is essentially similar to that in normal rats. However two important observations make the effect of nicotine in thyroidectomised rats different from that of the normal. Firstly, the significant reduction in basal blood glucose levels following thyroidectomy. This is appreciated in

view of the fact that thyroid hormones enhance metabolic rate [24]. Muller *et al* [25] showed that thyroid hormone increases glucose disposal *in vivo*.

Secondly, the peak value of blood glucose rises following injection of nicotine in thyroidectomised rats is significantly lower than normal. This seems to suggest that a normal and functional thyroid gland is necessary for the effect of nicotine on blood glucose to be fully elicited.

In this study, prazosin or propranolol when administered singly significantly reduced nicotine-induced hyperglycemia while a combination of the two drugs abolished nicotine induced hyperglycemia in the thyroidectomised rats. The present study therefore seems to suggest that both alpha and beta-receptors are involved in nicotine effect.

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