NORADRENALINE RELEASE BY NICOTINIC ACID

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Summary: In doses (from 100 *µg* to 1 *mg*) nicotinic acid produced positive inotropic and chronotropic action on isolated frog heart. This effect was blocked by pronethalol and guanethidine administration. This effect was not observed in reserpinised frogs. Repeated administration of the same dose of nicotinic acid caused development of tachyphylaxis, in frog's heart preparation. The observations indicate that nicotinic acid induced a release of noradrenaline in frog's heart.

On other preparations, such as isolated rabbit heart, rabbit's intestine and guinea pig seminal vesicles, nicotinic acid produced a nonspecific direct depresssant action.

Key words: nicotinic acid noradrenaline frog's heart

INTRODUCTION

Nicotinic acid (Pyridine-3 Carboxylic acid) is known to produce a transient fall in B.P. in man, cats and dogs but in rabbits, a rise in blood pressure was observed by Abdel-Aziz (1). This author suggested that the rise in B.P. in rabbits could be due to release of noradrenaline by nicotinic acid. There are also reports that a number of synthetic pyradine derivatives, structurally related to nicotinic acid, also bring about release of noradrenaline in frog's heart and other mammalain heart preparations (3,4). These observations indicate an involvement of adrenergic mechanisms in the actions of pyridine containing substances including nicotinic acid. It was therefore thought interesting to study the mechanism of some of these actions of nicotinic acid on various test objects.

MATERIALS AND METHODS

1) *Isolated frog's heart preparation:* The preparation as described by Burn (2) was used. The responses were observed on smoked drum with isotonic lever in twenty such experiments. The drugs were injected through a canula in the sinus venosus.

In 4 experiments, frogs were reserpinised with 2 *mg/kg* of reserpine, I.P. and after 48 hours, hearts were exposed.

2) *Isolated rabbit's intestine:* A 2 cms. piece of rabbits' ileum was mounted in 40 *ml* bath, containing mammalian Ringer Solution bubbled with O_2 gas. The temperature was maintained at 37°C by a thermostat. Contractions were recorded on smoked drum with isotonic frontal writing lever with a magnification 6 times and a basal tension of 0.5 *gm*. Responses were noted for 30 secs. The blocking drugs were incubated in the bath for 5 min. Eight such experiments were done.

3) *Isolated seminal vesicle of guinea pig:* Eight male guinea pigs weighing between 200-400 *gms* were used. Each seminal vesicle was mounted separately in 40 *ml* bath containing Kreb's solution bubbled with a mixture of 95% O_2 and 5% Co_2 gas. The temperature was maintained at 37°C by a thermostat. Responses were recorded on smoked drum with a magnification 8 times and a basal tension of 1 *gm*. Each response was recorded for 30 secs.

4) *Langendorff's preparation:* Six rabbits were used. Hearts were quickly isolated and perfused through canula in the aorta with mammalian Ringer solution at 37°C, oxygenated with continuous bubbling of O_2 gas. Responses were recorded on smoked drum.

Drugs used: Nicotinic acid powder (B.D.H.) noradrenaline bitartrate, adrenaline hydrochloride, Alderlin (Pronethalol), guanethidine, reserpine, phenoxy-benzamine, atropine sulphate, acetylcholine bromide and hexamethonium.

Stock solution of nicotinic acid was prepared fresh, every day, in distilled water.

RESULTS

1) *Isolated frog heart preparation:* Injection of nicotinic acid in a dose of 1 *mg* consistantly produced a significant increase in the heart rate and force of myocardial contraction (Fig. 1). In

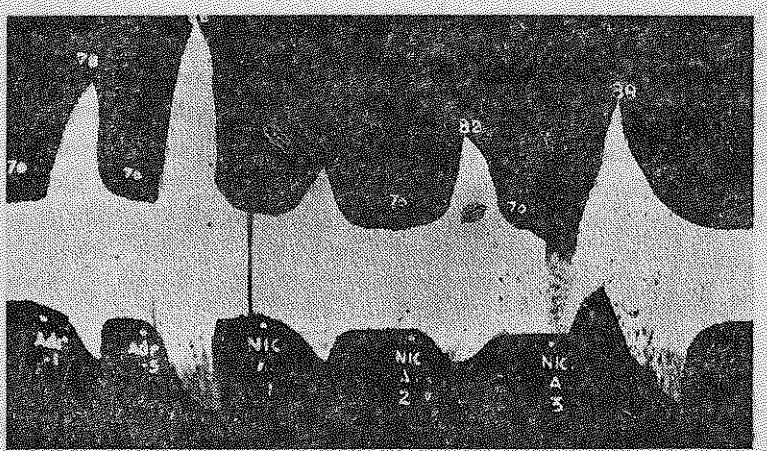

Fig. 1: *Isolated frog's heart:* Shows responses to adrenaline and nicotinic acid
Adr- Adrenaline 0.1 and 0.5 *ugms*.
Nic. A - Nicotinic acid 1, 2 & 3 (100 µ*gms*, 500 µ*gms* and 1 *mg* doses respectively).
Figures at the top denote heart rate, per minute.

a number of experiments, 1 *mg* dose of nicotinic acid produced initial transient inhibition followed by marked increase in the rate and force of heart (Fig. 1). The effect disappeared in 5 min. Higher concentrations (more than 2 *mgs* of nicotinic acid) always produced inhibition and diastolic arrest of the heart.

Repeated administration (every five min) of nicotinic acid (1 *mg*) always produced tachyphylaxis with increase in the initial inhibitory response (Fig. 2). The responses could be

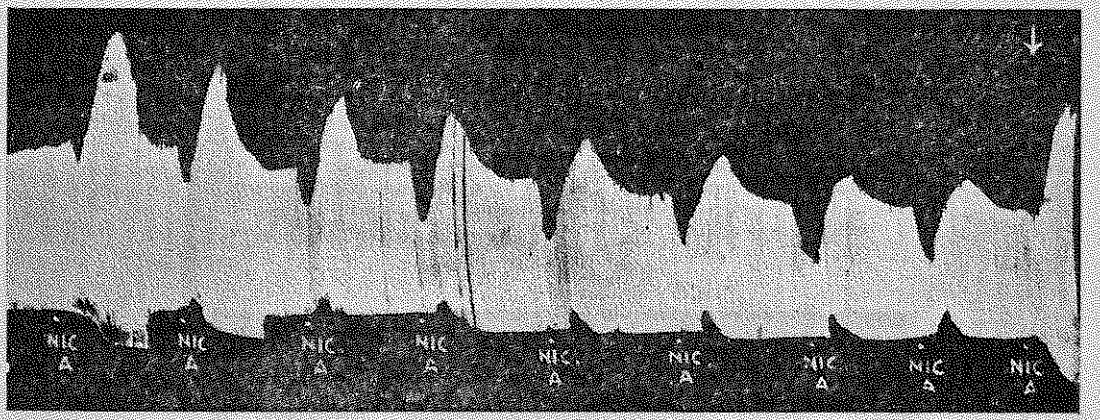

Fig. 2: *Isolated frog's heart:* Shows development of tachyphylaxis to repeated administration of nicotinic acid (1 *mg.*) The initial depression increased as the stimulation is decreased. At arrow, partial recovery of the response after 15 min of continuous perfusion of Ringer Solution.

restored completely within 1/2 to 1 hour of continuous perfusion of Ringer Solution (Fig. 2). In reserpinised hearts (4 expts.) no increase in the rate and force of heart to nicotinic acid was noted; only inhibition was seen. The inhibition was not blocked by atropine treatment. Guanethidine (100-400 μg) always produced a marked increase in the rate and force of heart and stimulant responses to nicotinic acid were completely blocked after guanethidine treatment (Fig. 3). Instead of stimulation only a depressant effect was noted (Fig. 3). Hexamethonium, a ganglion blocking agent, did not modify the stimulant effect of nicotinic acid on the Frog's heart.

Pronethalol (a beta blocking agent) in doses of 5-10 μg blocked the responses to adrenaline as well as to nicotinic acid (Fig 4).

2) *Rabbit's ileum preparation:* Isolated rabbit ileum showed relaxation to nicotinic acid (50-200 $\mu gs/ml$) (Fig. 5).

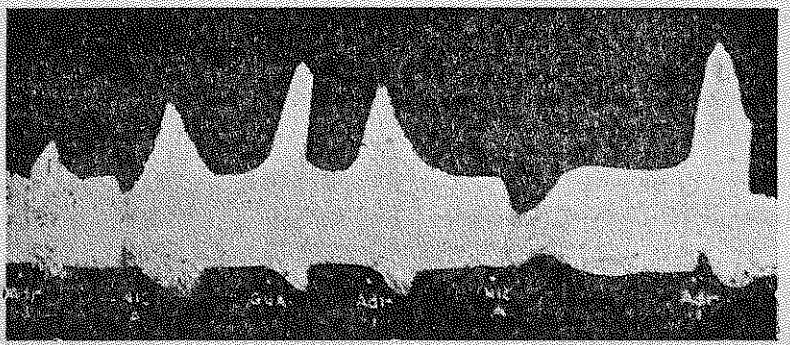

Fig. 3: Shows positive ionotropic response to Adrenaline (.1 μgm) and nicotinic acid (1 *mg*). At Gua, Guanethidine (400 μgms) was injected, it produced a brisk response like adrenaline. After Guanethidine, adrenaline (.1 μgm) response was potentiated and the response stimulant of Nicotinic acid was abolished, only inhibition was seen.

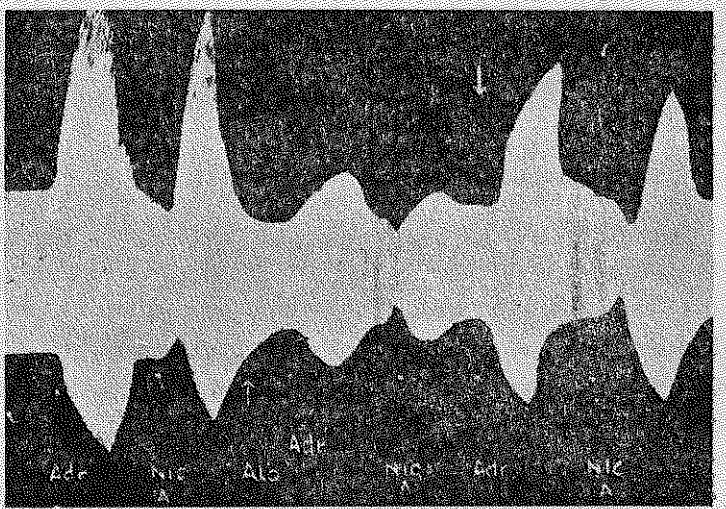

Fig. 4: Shows responses to adrenaline (1 μgm) and nicotinic acid (1 *mg*) on frog's heart. At ald. Alderin (10 μgm) was injected. The responses of adrenaline and nicotinic acid were significantly blocked. After 15 min, partial recovery to Adrenaline & nicotinic acid was seen. Adr. — Adrenaline; Nic. A — Nicotinic acid.

Neither guanethidine (100-200 $\mu g/ml$) nor adrenergic blockers like pronethalol (1-10 $\mu g/ml$) and phenoxybenzamine (0.1 to 1 $\mu g/ml$) could block the relaxant responses to Nicotinic acid (Fig. 5).

3) *Other preparations:* On isolated rabbit heart, nicotinic acid (100 *µgm* to 4 *mg*) produced inhibitory effect. This inhibitory effect was dose dependant and it was not abolished by atropine treatment.

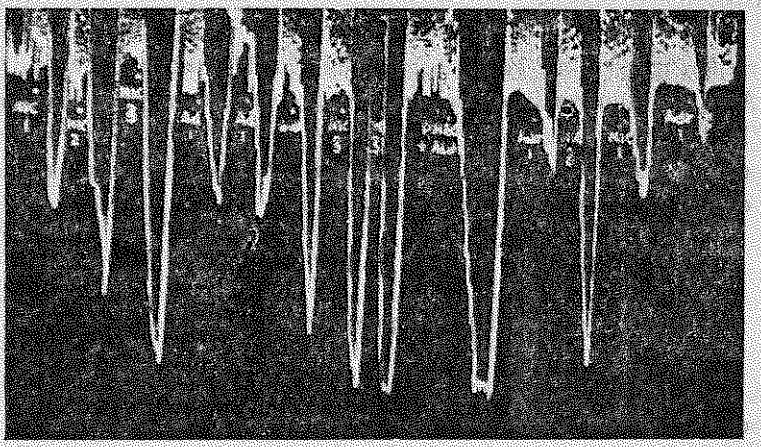

Fig. 5: *Isolated Rabbit's intestine:* Shows relaxant responses to Nicotinic acid 1,2 3, (50,100 and 200 *µgms/ml*) and adrenaline (1 *µg/ml*). At Gua, Guanethidine was added, relaxation was noted. Nicotinic acid responses were unmodified after guanethidine.
At Phe + Ald (phenoxybenzamine & Alderlin 0.1 *µgms* & 5 *µg/ml* respectively were added; produced relaxation of intestine.
The responses of adrenaline were partially blocked but those of nicotinic acid were unmodified.
Nic. — Nicotinic acid
Ad — Adrenaline
Gua — Guanethidine
Phe + Ald — Phenoxybenzamine + Alderlin

On the seminal vesicle of guinea pig, no response to nicotinic acid, (100 *µgs* to 1 *mg/ml*) alone, was seen, but in these concentrations, nicotinic acid nonspecifically decreased the responses to adrenaline, noradrenaline and acetylcholine.

DISCUSSION

From the results of our study, it is clear that nicotinic acid produced two types of actions on various preparations studied.

The positive inotropic and chronotropic effect on frog's heart may be due to release of endogenous noradrenaline, since guanethidine and propranalol completely abolished this response to nicotinic acid. Secondly, this action was not seen in reserpinised frogs. Further, tachyphylaxis was observed after repeated administration of nicotinic acid. Thus we have confirmed that nicotinic acid does not differ in it's actions from other synthetic pyridine analogues (3 and 4).

The inhibitory effect to higher doses of nicotinic acid on frog's heart and on other preparations such as rabbit's heart, rabbit intestine and guineapig's seminal vesicle appears to be a nonspecific direct depressant action on the muscle and seems to be similar to one exerted on the blood vessels.

Species variation to nicotinic acid responses on blood pressure has already been pointed out by Abdel - Aziz (1). Our results on isolated frog's heart further confirms the assumptions of Abdel-Aziz (1), that the rise in blood pressure in rabbits with nicotinic acid administration, may be due to release of noradrenaline. However nicotinic acid failed to produce release of catecholamines on the rabbit's isolated heart preparation.

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