A STUDY OF THE EFFECT OF DOPAMINE ON ADRENERGIC RECEPTORS

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Dopamine has been found to be present at various sites in the body (1). It acts as a precursor in the biosynthesis of norepinephrine and has also been ascribed a role of being a neurotransmitter (2). The effect of dopamine on the alpha adrenergic receptors is well established (3), but there are controversial reports regarding its beta receptor activity. Katz et al. (4) found that cyclopropane-dopamine and halothane-dopamine cardiac arrhythmia is blocked by H 56/28, a beta adrenergic blocking agent. However, the specificity of beta adrenergic blockers (especially pronethalol) has been questioned since some of them have local anaesthetic and quinidine like effects, which may account for their anti-arrhythmic action (5-9). Eble (3) reported, that dopamine produces a depressor response after pre-treatment with alpha blocking agent, which is not blocked by a beta adrenergic blocking agent. McNay and Goldberg (10) pointed out that some of the effects of dopamine might be exerted via “dopamine receptors” which are different from beta receptors. It was thus of interest to study the beta adrenergic activity of dopamine by using propranolol, a specific beta adrenergic blocking agent.

Sympathomimetic amines act either directly or indirectly through the release of catecholamines or by both ways. Earlier dopamine was regarded to act directly on the adrenergic receptors (11-13). Blinks (14) also regarded it as a directly acting amine since he failed to observe a decrease in potency of dopamine after pretreatment with reserpine. It is also not known whether the ability of dopamine to produce arrhythmia is a direct effect or an indirect one due to release of norepinephrine (15). Although dopamine is thought not to release norepinephrine from blood vessel walls, there is evidence that it releases norepinephrine from myocardium (16). However, Tsai et al. (17) showed that dopamine has both direct and indirect effects on isolated guinea pig atria and nictitating membrane of cat. Hence it was also of interest to study whether dopamine acts directly or through the release of catecholamines or by both mechanisms. Lastly the drug parameters like intrinsic activity and affinity of dopamine has been compared with that of norepinephrine.

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METHODS

The effect of dopamine was studied on the isolated rabbit's ileum, rabbit's heart and rat's vas deferens taken from normal and reserpinized (5 mg/kg i.p. for two days) animals.

Rabbit ileum: A piece of ileum 6 cm long was suspended in Dale's isolated organ bath filled with Tyrode solution at 37°C and bubbled with air. The contractions of the intestine were recorded on smoked kymograph paper. Sufficient time was allowed to stabilize the gut after which the effect of dopamine was seen. The response to norepinephrine was always taken as control. Dibenzyline (3 μg/ml) and propranolol (0.3 μg/ml) were used to find the nature of dopamine response.

Rabbit heart: The rabbits were killed by giving a blow on the head, the heart was quickly removed and mounted according to the modified technique of Langendorff in Anderson's coronary perfusion apparatus. The heart was perfused through the aorta by Tyrode solution at 37°C. The amplitude of contraction of the heart was recorded on smoked kymograph paper. Sufficient time was allowed to stabilize the preparation. Drugs were injected through a fine capillary in the perfusion fluid near the tip of cannula attached to the aorta. The effect of dopamine (1 mg) and norepinephrine (10 μg) were observed both in presence and absence of propranolol (0.3 μg/ml).

Rat vas deferens: The rat vas deferens was suspended in Dale's isolated bath filled with Krebs-Henseleit solution and bubbled with air. A number of cumulative dose response curves of dopamine alternately with that of norepinephrine were obtained in reserpinized and non-reserpinized rat vas deferens on smoked kymograph paper. The mean heights of contractions were converted into percentages of the maximal contractions and were plotted against log molar concentrations of the drug. The affinity and intrinsic activity have been calculated from individual dose response curves as described by Van Rossum (18).

RESULTS

Rabbit intestine: Dopamine produced relaxation of the intestine of normal as well as of reserpinized rabbits. There was no complete tachyphylaxis in the relaxant effect

![Fig. 1. Effect of dibenzyline (3 μg/ml) and propranolol (0.3 μg/ml) and dopamine (1.3 μg/ml) on isolated rabbit's ileum. Note that the relaxation produced by norepinephrine and dopamine is incompletely blocked by dibenzyline alone but completely blocked when propranolol is also added to the bath.]
Fir 2. Effect of propranolol on the responses of norepinephrine (10 pg) and dopamine (1 mg) on isolated rabbit's heart. Note that the positive inotropic action of norepinephrine and dopamine are completely blocked by propranolol (0.3 µg/ml).

of dopamine. The relaxation produced by equipotent doses of norepinephrine (0.1 µg/ml) and dopamine (1.3 µg/ml) in unreserpinized rabbit's ileum were partially blocked by dibenzyline (3 µg/ml) and completely when propranolol (0.3 µg/ml) was also added to the bath fluid (Fig. 1).

*Rabbit* heart: Dopamine produced an increase in amplitude of contraction of the heart both in normal and reserpinized rabbits. There was no complete tachyphylaxis in the responses of dopamine. The positive inotropic action of equipotent doses of norepinephrine (10 µg) and dopamine (1 mg) in unreserpinized rabbit's heart were completely blocked by propranolol (0.3 µg/ml) (Fig. 2).

*Rat vas deferens:* Both in normal and reserpinized rats dopamine produced contraction of the vas deferens. There was no tachyphylaxis on repeated doses.

The log dose percent response curves of dopamine and norepinephrine in normal and reserpinized rat vas deferens preparations are plotted in Fig. 3. There is an increased sensitivity to norepinephrine due to reserpinization. This increased sensitivity is more marked with the lower doses as evidenced by greater shifting of the bottom portion of the curve to the left. This may be due to the fact that with cumulative dose method of taking the responses, some of the norepinephrine is taken up by the tissues
and thus giving less supersensitivity to the higher doses of norepinephrine. Dopamine has been found to be less active than norepinephrine as evidenced by the presence of dopamine curve parallel to the right of norepinephrine curve. Reserpinization further reduces the potency of dopamine as shown by the shifting of the curve of dopamine to the right. The presence of the bottom portion of the curve of dopamine in reserpinized rat vas deferens to the left of the normal dopamine curve, might be due to supersensitivity to the direct effect of dopamine and that this supersensitivity masks the abolition of indirect effects.

The affinity (pD₂ value) of dopamine and norepinephrine, which is connected with the negative logarithm of the dose that produces 50% of the maximum effect (18), as calculated from individual dose response curves, is given in Table 1.

**DISCUSSION**

Dopamine produced relaxation of the rabbits intestine which is not completely blocked by dibenzyline or propranolol but completely blocked when both are added together. This shows that dopamine acts on beta adrenergic receptors in addition to alpha adrenergic receptors. This is further shown by the fact that the positive inotropic actions of dopamine on isolated rabbit heart are completely blocked by propranolol. As the heart contains mainly beta receptors and propranolol is a specific beta adrenergic blocking agent, it indicates that dopamine does act on beta adrenergic receptors. Our findings do not support the view of McNay and Goldberg (10) who pointed out that some of the effects of dopamine might be exerted via "dopamine receptors" which are different from beta receptors.

The affinity of dopamine (pD₂=4.95±0.05 S.E.) to combine with the receptor is less than that of norepinephrine (pD₂=5.07±0.05 S.E.) showing that it is a weaker agonist. The affinity of norepinephrine increases (pD₂=5.10±0.07 S.E.) due to reserpinization which indicates supersensitivity. The pD₂ value for norepinephrine in reserpinized rat vas deferens is not statistically significant from that of normal. This is due to the fact that these affinities have been calculated at the 50% dose level. As already pointed out, that by cumulative dose method of taking responses, there is a gradual uptake of norepinephrine and hence with the increase in dose the norepinephrine curves in reserpinized and non-reserpinized tissue come close to each other. However, the affinity of dopamine is lowered.
(pD₂ = 4.61 ± 0.07 S.E.) due to reserpinization which indicates that a part of its action is exerted through the release of catecholamines. The effects of dopamine do not appear to be due to its conversion into norepinephrine since pretreatment with reserpine not only depletes endogenous norepinephrine stores but also antagonizes the conversion of dopamine to norepinephrine (19). Moreover Tsai et al. (17) have shown that pretreatment with disulfiram which blocks beta hydroxylation of dopamine had no significant effect on the responses to dopamine on isolated guinea pig atria.

Thus dopamine possess both alpha and beta adrenergic activity and its effects are both direct and indirect through the release of catecholamines.

SUMMARY

The effect of dopamine has been studied on isolated rabbits ileum, rabbits heart and rat vas deferens preparation. Dopamine has been shown to act on beta adrenergic receptors in addition to alpha adrenergic receptors. The affinity of dopamine is 4.95 ± 0.05 S.E. in normal and 4.61 ± 0.07 S.E. in reserpinized rat vas deferens preparation which indicates that it acts both by direct and indirect mechanism.

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