Demethylimipramine (Desipramine), an α-Adrenergic Blocking Agent

Norepinephrine accumulates in cell cytoplasm by a transport mechanism, called the 'membrane pump' by CARLSSON[1], and from there it is normally taken up rapidly by storage granules. When the latter mechanism is blocked by reserpine, norepinephrine is metabolized by monoamine oxidase in cell cytoplasm. The 'membrane pump' can be effectively blocked by imipramine or its metabolites[2,3], the most potent of which is demethylimipramine (desipramine). Thus LOEW[4] showed that desipramine potentiated the pressor effect of epinephrine in rabbit, at low doses of 0.3 mg/kg, while KAUMAN, ZUBERBÜHLER and TAQUINI[5] showed the same potentiation in dog. They showed that prior reserpinization did not alter this, but that prior administration of α-adrenergic blocking agents abolished the potentiation. More recently, HRDINA and GARATTINI[6] showed that desipramine and cocaine increased the pressor response to norepinephrine on isolated perfused renal arteries of rat. They suggested that the mechanism of this potentiation is due to inhibition of uptake of the catecholamine by the arterial wall nerve endings. CARLSSON[1] has mentioned a paradox of the actions of desipramine in that it causes orthostatic hypotension, although it inhibits an important mechanism for inactivation of catecholamines and thus potentiates the effect of sympathetic nerve stimulation.

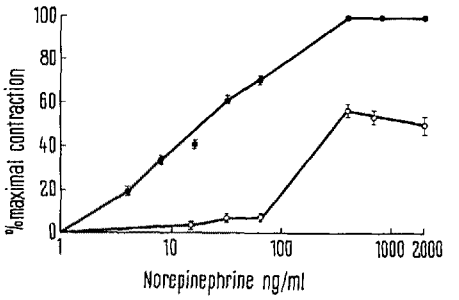
Desipramine was used for studies on interrelationships between catecholamines and angiotensin on isolated blood vessels. Spirally cut aortic strips from normal or reserpinized rabbits were prepared according to FURCHGOTT and BHADRAKOM[7]. Animals were given 2.5 mg/kg reserpine the first day, 5.0 mg/kg the second day, and the blood vessels were removed on the third day. The strips were mounted in a 25 ml muscle bath in Krebs' solution, and aerated with 95% O_2, 5% CO_2. Contractions were recorded isotonically and were expressed as % maximal contraction[8], and standard error calculated.

Desipramine itself neither relaxed nor contracted rabbit aorta. However, 0.5 μg/ml partially antagonized, and 1.0 μg/ml inhibited the contractile response to norepinephrine. As seen in the Figure, the dose-response curve of norepinephrine indicated decreased sensitivity following 0.5 μg/ml desipramine, which can be interpreted as competitive antagonism. The maximal response was also decreased.

Low doses of desipramine were synergistic with phentolamine; the α-adrenergic blocking effects being additive. At a dose that completely abolished responses to norepinephrine (1 μg/ml) desipramine partially inhibited response to serotonin (40 ng/ml), but had no effect on responses to angiotensin (1–10 μg/ml).

We have previously shown[9] that a potentiated response to angiotensin could be obtained from a reserpinized blood-vessel strip, and that this potentiated response was reversed by re-introduction of norepinephrine into storage granules. When this experiment was repeated, using desipramine (0.5 μg/ml) before equilibration with norepinephrine, the increased response to angiotensin was retained and norepinephrine did not reverse the potentiation, indicating that desipramine inhibits the 'membrane pump' and the uptake of norepinephrine into cell cytoplasm; however, it also inhibits direct contractile response to the catecholamine. This inhibition was not due to a change in the contractile properties of vascular smooth muscle, since the strip still responded to angiotensin. The partial inhibition of serotonin and complete inhibition of norepinephrine can be explained by an α-adrenergic blocking action of desipramine. A structurally similar compound, azapetin (Ilidar), is a well-known α-adrenergic blocking agent. This could explain the paradox mentioned by CARLSSON[1], in that desipramine, although inhibiting an important mechanism for inactivation of catecholamines, produces orthostatic hypertension. This is possibly due to the α-adrenergic blocking action of the drug preventing the potentiated response of sympathetic nerve stimulation.

This leads to the speculation that in vascular smooth muscle, the α-adrenergic receptor and the 'membrane pump' are either the same, or are on the same site in the cell membrane. Compounds like desipramine can inhibit both simultaneously, while others like phentolamine only inhibit the adrenergic receptor[10].



Dose-response curve of spirally cut rabbit aorta to norepinephrine. Cross bar represents standard error in 25 experiments. ●—● = norepinephrine; o—o = norepinephrine in the presence of 0.5 μg/ml desipramine.

Résumé. La déméthylimipramine (désipramine) inhibe la contraction provoquée par la norépinéphrine dans les bandelettes spirales des vaissaux du lapin, mais non celle produite dans les mêmes vaissaux par la sérotonine ou l'angiotensine. Son action est synergique avec celle de la phentolamine. On suppose que la désipramine possède à la fois une action inhibant la captation («uptake») des catécholamines par les terminaisons nerveuses et une autre bloquant les sites récepteurs α-adrénergiques.

R. K. TÜRKER and P. A. KHAIRALLAH

Research Division, Cleveland Clinic, Cleveland (Ohio 44106, USA), October 24, 1966.

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