Mechanism of K^+-induced release of cytoplasmic noradrenaline from adrenergic nerves

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Wakade and Kirpekar (1974) reported that K^+ released noradrenaline (NA) from reserpine-pretreated and MAO-inhibited vasa deferentia of guinea pigs by a Ca^{++}-independent process. In the present study, the mechanism of this effect has been further examined.

As described previously (Paton, 1973), atria, from reserpine-pretreated rabbits, were exposed to pargyline (5×10^{-4} M for 30 min) and tropolone (10^{-4} M), and then to 5×10^{-7} M [^{3}H]-(−)-NA for 60 minutes. Tissues were blotted and transferred every 5-10 min to fresh media at 37°C. Tissues were exposed to elevated K^+ for 40 min after 50 min of efflux. At 90 min tissues were removed and their ^{3}H content determined. Media had the following composition: (a) control medium (mM): NaCl, 140; KCl, 5.0; $CaCl_2$, 1.5; $MgCl_2$, 1.2; Tris-HCl, 20; and (b) medium with elevated K^+: as above except NaCl, 100; KCl, 65.

Efflux of [^{3}H]-NA was not accelerated by 25 mM KCl. However, 45-85 mM KCl caused a progressive increase in [^{3}H]-NA efflux. In subsequent studies, the effects of 65 mM K^+ were examined. Efflux was also accelerated by 65 mM RbCl and CsCl, the relative potencies being $K^+ = Rb^+ > Cs^+$.

The accelerative effect of 65 mM KCl on [^{3}H]-NA efflux was not altered by 10^{-5} M phentolamine, 10^{-7} M oxymetazoline, 5.6×10^{-5} M indomethacin, 10^{-4} M procaine or 10^{-4} M lidocaine, but was significantly inhibited by 1.5×10^{-5} M cocaine and 10^{-6} M desipramine, and was abolished when tissues were loaded with [^{3}H]-NA in the presence of 3×10^{-5} M cocaine, 10^{-4} M hydrocortisone and 10^{-4} M oxytetracycline.

K^+-induced release of NA from untreated tissue (i.e., with normal vesicular storage of NA) is Ca^{++}-dependent and is subject to α-receptor feedback inhibition (Kirpekar and Wakade, 1968; Stjärne, 1973; Starke & Montel, 1974). By contrast, this study and that of Wakade and Kirpekar (1974) has shown that elevated K^+ accelerates the efflux of [^{3}H]-(−)-NA from extragranular, cytoplasmic sites in peripheral adrenergic nerves by a process that is not subject to α-receptor or prostaglandin-mediated feedback inhibition, does not require Ca^{++}, and is inhibited by cocaine and desipramine. These findings show that the process does not result from exocytosis of NA. It is suggested that raising the external K^+ concentration caused membrane depolarization and that this accelerated the loss of NA via a cocaine- and desipramine-sensitive carrier. Ouabain, omission of external K^+ and metabolic inhibition also accelerated the efflux of [^{3}H]-NA and these effects were all inhibited by cocaine (Paton, 1973). These procedures also produce membrane depolarization. It has been proposed that the membrane potential is also involved in the uptake (or influx) of NA in adrenergic nerves (Holz, Deguchi & Axelrod, 1974; White, 1975).

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