The effects of ketamine on noradrenergic transmission and the response to noradrenaline in rat smooth muscle

A.J. BYRNE, T.E.J. HEALY & D.R. TOMLINSON

Department of Surgery (Anaesthesia) and Department of Physiology and Pharmacology, Queen's Medical Centre, University Hospital, Clifton Boulevard, Nottingham, NG7 2UH

Ketamine depresses responses to sympathetic nerve stimulation but potentiates responses to exogenous noradrenaline in the cardiovascular system of the rabbit (McGrath & MacKenzie, 1977). We have found that ketamine potentiates the response of rat isolated atria to noradrenaline and to noradrenergic nerve stimulation (Byrne, Tomlinson & Healy, 1979). These experiments are complemented by the present study in an attempt to elucidate the mechanisms of the effects of ketamine on noradrenergically innervated tissues.

Hepatic portal veins and vasa deferentia were removed from freshly killed Wistar rats (300 to 450 g) and suspended in organ baths containing Krebs' solution gassed with 95% O_2/5% CO_2 at 37°C. Preparations were either subjected to field stimulation of their intramural nerves via parallel platinum wire electrodes (140 V, 200 μs, 10 s trains for veins, 30 s trains for vasa, 1–20 pulses/s) or were used to obtain log dose-response curves for exogenous noradrenaline.

Ketamine (3×10^{-5} M) potentiated the response of veins and vasa to nerve stimulation at 1–5 pulses/s ($P < 0.05$, $n = 6$) but the responses to higher frequencies were unchanged. Ketamine also shifted to the left the log. dose-response curve for noradrenaline ($P < 0.05$, $n = 6$). The lower doses of noradrenaline were potentiated to a greater extent than the higher doses. Ketamine also increased the duration of the response to nerve stimulation, this effect being particularly marked in the portal vein.

Ketamine showed no sympathomimetic effects so that further experiments were performed to test for Uptake 1 blockade or presynaptic α-adrenoceptor blockade either of which might be implicated to account for the above findings.

Yohimbine (1×10^{-7} M), which blocks presynaptic α-adrenoceptors in the vas (Marshall, Nasmyth, Nicholl & Shepperson, 1978) potentiated the response of the vas to low frequency nerve stimulation but did not affect the response to noradrenaline. Addition of ketamine (3×10^{-5} M) to the bath, in the continued presence of yohimbine, further potentiated the response to nerve stimulation and increased the response to exogenous noradrenaline. In contrast pancuronium bromide, which blocks Uptake 1 (Tomlinson, 1979), caused a potentiation of the response to either nerve stimulation or to noradrenaline which was not augmented by addition of ketamine to the pancuronium already present.

Neuronal uptake (Uptake 1) of α-methyl noradrenaline in iris, hepatic portal vein, vena cava and mesenteric arterioles from reserpinised (2 mg/kg) mice was studied by a fluorescence histochemical method (see Tomlinson, 1979). Uptake of α-methyl noradrenaline was reduced by a ketamine concentration of 3×10^{-5} M and blocked completely at 2×10^{-4} M.

These findings indicate that ketamine acts as an inhibitor of neuronal uptake of noradrenaline, thereby potentiating the response of vas and portal vein to noradrenaline. The depression of the response to nerve stimulation reported by others and seen at higher doses of ketamine (1×10^{-4} M) in our experiments is presumably a manifestation of neuronal depression and a reflection of the anaesthetic property of the drug.

Financial assistance from Parke Davis & Co. is gratefully acknowledged.

References

BYRNE, A.J., TOMLINSON, D.R. & HEALY, T.E.J. (1979). Effects of ketamine on autonomic transmission in rat isolated atria. *Br. J. Anaesth.* (In press).

MARSHALL, I., NASMYTH, P.A., NICHOLL, CLAIRE G. & SHEPPERSON, N.B. (1978). α-Adrenoceptors in the mouse vas deferens and their effects on its response to electrical stimulation. *Br. J. Pharmac.* **62**, 147–151.

MCGRATH, J.C. & MACKENZIE, J.E. (1977). The effects of intravenous anaesthetics on the cardiovascular system of the rabbit. *Br. J. Pharmac.*, **61**, 199–212.

TOMLINSON, D.R. (1979). On the mechanism of pancuronium-induced supersensitivity to noradrenaline in rat smooth muscle. *Br. J. Pharmac.* **65**, 473–479.