γ-Aminobutyric acid reduces the evoked release of [^{3}H]-noradrenaline from sympathetic nerve terminals

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Activation of γ-aminobutyric acid (GABA) receptors in peripheral sympathetic ganglia produces a neuronal depolarization (Bowery & Brown, 1974; Adams & Brown, 1975). Recent work by Brown & Marsh (1978) has indicated that the receptors are not confined to the neuronal cell body but continue along the axon. The aim of the present study was to determine whether they are also present on the sympathetic nerve terminals. If GABA depolarizes the nerve terminals this might lead to a decrease in evoked transmitter release. We have therefore examined the effect of GABA on the basal and evoked release of accumulated [^{3}H]-noradrenaline from isolated atria and vas deferens of the rat.

The tissues were incubated for 40 min at 32°C (atria) or 37°C (vas deferens) in Krebs-Henseleit solution containing [^{3}H]-noradrenaline (0.4 μM; 5 Ci/mmole, Radiochemicals Amersham) and then superfused with radioactive-free solution at 0.45 ml/min. The tritium contents of 4 min superfusate samples were determined by liquid scintillation spectrometry. All solutions contained ascorbic acid (100 μM) and iproniazid (0.5 mM) to reduce noradrenaline catabolism.

The addition of GABA (concentrations up to 1 mM) to the superfusing solution did not affect the basal release of tritium from the atria. However, when applied for 30–60 s before transmural stimulation (rectangular pulses 3 Hz, 0.5 ms, 10V for 1 min) GABA reduced the subsequent increase in tritium overflow. This reduction was small (about 10%) and variable.

Phentolamine (2.5 μM) or yohimbine (2.5 μM) added to the superfusion solution increased the evoked release by 2–4 fold without affecting the basal release (cf. Langer, Adler-Graschinsky & Giorgio, 1977). When GABA was now applied for 30 s a much larger and less variable depression in the evoked release occurred. This effect was dose dependent (0.3–300 μM, ED_{50} 3 μM) producing a maximal reduction of 50.1 ± 2.18% ($n = 5$) at 100–300 μM. Superfusion with GABA for longer periods (15–30 min) before stimulation only marginally reduced (~10%) the evoked release. This brief action is comparable with the transient depolarization previously described in ganglia (Bowery & Brown, 1974).

Pretreatment of the atria with the GABA antagonists (+)-bicuculline methochloride (300 μM), picrotoxin (170 μM), isopropylbicyclophosphate (200 μM), leptazol (700 μM), penicillin (2 mM), or the convulsant bemegride (1 mM) failed to modify the response to GABA. The GABA analogues β-hydroxy-GABA and muscimol mimicked the action of GABA although both were less active (0.01–0.1). Other analogues, taurine (0.8 mM), β-alanine (10 mM), 3-aminopropane sulphonic acid (0.6 mM), imidazole acetic acid (8 mM), isoguvacine (0.5 mM), isonipecotic acid (8 mM), glycine (1.5 mM), β-aminobutyric acid (10 mM), guanidinopropionic acid (0.8 mM) and guanidoacetic acid (9 mM) were all inactive. Carbachol (33 μM) applied for 1 min before stimulation reduced or abolished the increase in tritium overflow. Atropine (0.14 μM) prevented or reduced this effect of carbachol but was ineffective against GABA.

Results similar to those obtained in atria were also observed in vasa deferentia and in addition GABA reduced the twitch response to stimulation.

In conclusion, we have detected an action of GABA on sympathetic nerve endings which leads to a decrease in evoked [^{3}H]-noradrenaline output. However, the 'receptor' surprisingly appears to differ in its chemical specificity from that producing neuronal depolarization.

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Presynaptic effects of γ-aminobutyric acid in isolated rat superior cervical ganglia

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We have recently reported that GABA depolarizes preganglionic sympathetic fibres (Brown & Marsh, 1978). A comparable effect on preganglionic terminals might reduce transmitter release. The present experiments were designed to test this.

Superior cervical ganglia with attached pre- and post-ganglionic nerve trunks were isolated from