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Effects of γ-aminobutyric acid on the potassium and tyramine induced release of [^{3}H]-noradrenaline from rat occipital cortex slices

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Both in the peripheral and in the central nervous system the release of noradrenaline (NA) is regulated through a negative feed-back mechanism mediated by presynaptic alpha-adrenoceptors (for reviews, see Langer, 1974, 1977; Starke, 1977). In addition the release of central neurotransmitters can be modified by other putative neurotransmitters through presynaptic mechanisms (Jessel & Iversen, 1977; Arbilla & Langer, 1978).

Recently, it was reported by Taube, Starke & Borowski (1977) that exogenous gamma aminobutyric acid (GABA) does not affect the K^+-induced release of [^{3}H]-NA from rat cerebral slices. On the other hand, the turnover of NA in the rat brain is increased after the administration of GABA systemically and intracerebroventricularly (Biswas & Carlsson, 1977a, b). In the present experiments the effects of GABA were re-examined for the release of [^{3}H]-NA induced by two different concentrations of potassium and by tyramine.

Occipital cortex slices of 0.3 mm thickness were obtained from male rats (150 to 200 g) and prelabelled with [^{3}H]-NA (Farah, Adler-Graschinsky & Langer, 1977). The percentage of total tissue radioactivity released by a 1 min exposure to 20 mM K^+ in the controls was 4.03 ± 0.65 ($n = 8$) during the first period of stimulation (S_1) and 4.74 ± 1.10 ($n = 8$) for the second stimulation (S_2) obtained 45 min after S. The ratio S_2/S_1 was 1.09 ± 0.10 ($n = 8$). Under these conditions the release of [^{3}H]-NA elicited by K^+ was entirely calcium-dependent (Arbilla & Langer, 1978). When exogenous GABA was added prior to S_2 there was a concentration-dependent increase in the release of [^{3}H]-NA induced by K^+. In the presence of 100 μM GABA the ratio S_2/S_1 was 1.47 ± 0.13 ($n = 6$, $P < 0.02$) and for 300 μM GABA the ratio S_2/S_1 was 2.22 ± 0.12 ($n = 8$, $P < 0.001$). During exposure to GABA (1 mM) the release of [^{3}H]-transmitter was also increased ($S_2/S_1 = 2.77 \pm 0.45$, $n = 6$, $P < 0.005$). The enhancement in [^{3}H]-NA release obtained in the presence of GABA (300 μM) was not antagonized by bicuculline (1 and 10 μM) or by picrotoxine (10 μM) under conditions in which the blocking agents did not by themselves affect the K^+-induced release of [^{3}H]-NA.

When [^{3}H]-NA release was elicited by a 1 min exposure to a higher concentration of K^+: 35 mM, the fraction of the total tissue radioactivity released was $32.3 \pm 1.3\%$ ($n = 6$). The release of the labelled neurotransmitter elicited by K^+ (35 mM) was not affected by either 300 μM or 1 mM GABA.

In contrast to the K^+-induced depolarization, tyramine displaces NA from vesicular storage sites through a calcium-independent mechanism. Consequently, it was considered of interest to examine the effects of exogenous GABA on [^{3}H]-NA release induced by tyramine. In the controls, exposure to tyramine (0.6 μM) produced a release of $8.5 \pm 1.5\%$ of total tissue radioactivity in S_1 ($n = 4$). The release of [^{3}H]-NA induced by tyramine was not enhanced by either 300 μM or 1 mM GABA.

The effects of exogenous GABA were also studied on the release of total radioactivity induced by nerve stimulation in a peripheral tissue, the isolated nerve-muscle preparation of the cat nictitating membrane, as described by Langer & Luchelli-Fortis (1977). Nerve stimulation was applied at 4 Hz for 5 min and with supramaximal voltage. In the controls the ratio of [^{3}H]-transmitter overflow between two consecutive periods of nerve stimulation, S_2/S_1 was 1.06 ± 0.10 ($n = 13$). Exogenous GABA (10, 30, 100 and 300 μM) added 15 min before S_2 did not modify either the spontaneous or the stimulation-induced release of the tritiated neurotransmitter.

In summary, GABA enhances the K^+-induced release of [^{3}H]-NA from the rat occipital cortex while it fails to modify the release of the labelled transmitter induced by tyramine. Recently, Stoof & Mulder (1977) reported a similar effect of endogenous GABA on the K^+-induced release of dopamine from the rat striatum. In contrast to the results obtained in the central nervous system, GABA did not affect NA release elicited by nerve stimulation in the isolated nerve-muscle preparation of the cat nictitating membrane.

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Catalytic inhibitors of GABA-transaminase as anticonvulsants in baboons with photosensitive epilepsy

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Two catalytic inhibitors of GABA-transaminase, γ-acetylenic GABA (4-amino-hex-5-ynoic acid) and γ-vinyl-GABA (4-amino-hex-5-enoic acid) block sound-induced seizures in mice (Schechter, Tranier, Jung & Böhlen, 1977) at 41 mg/kg and 990 mg/kg i.p., respectively.

We have tested these compounds for anticonvulsant action and acute toxicity in baboons from Senegal, *Papio papio*, naturally showing photosensitive epilepsy, both with and without priming with a subconvulsant dose of allylglycine (Meldrum, Horton & Toseland, 1975).

Complete protection against photically-induced seizures or generalized myoclonus was seen after γ-acetylenic-GABA (160–200 mg/kg i.v.) or γ-vinyl-GABA (450–950 mg/kg i.v.). Maximal protection occurred 3–8 h after injection; partial protection persisted for 24 hours. Toxic signs characteristic of classical anticonvulsant drugs (i.e. nystagmus and ataxia) were not seen.

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