1 μg) contracted rabbit aorta, dog saphenous vein and guinea-pig lung strip, but had little or no effect on the other preparations.

PGH_2 was a potent agonist on all the preparations examined; these effects may have been mediated either directly or indirectly by conversion to other biologically active prostanoids (Bunting, Gryglewski, Moncada & Vane, 1976). In contrast TXA_2 and U-46619 were potent agonists on rabbit aorta, dog saphenous vein and guinea-pig lung only. U-46619 therefore appears to be a selective TXA_2-like agonist; if this is so it could prove to be valuable in the study of the biological actions of TXA_2 since, unlike TXA_2, U-46619 is stable.

PGH_2 and sheep platelet microsomes were supplied by Dr. P.J. McCabe of the Biochemistry Department, Glaxo Group Research, Ware Division.

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The effect of GABA on the conductance of Ascarid muscle

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Del Castillo, De Mello & Morales (1964a) have described the hyperpolarizing effect of γ-aminobutyric acid (GABA) on the membrane potential of *Ascaris* muscle. The aim of the present experiments was to describe the effect of GABA on the conductance of *Ascaris* muscle.

Recordings were made from the bag region of the *Ascaris* muscle cells using two potassium-acetate filled microelectrodes for separate current injection and voltage recording. The preparation was perfused constantly with cool (22°C) Ringer (Del Castillo *et al.*, 1964b) to abolish spontaneous depolarizations of the pacemaker and permit the recording of stable resting potentials. The effect on the input conductance was measured from the slope of the current voltage plots observed in the different concentrations of GABA.

The resting membrane potential recorded in the bag region was 31 ± 1 mV, mean ± s.e. mean ($n = 17$). The resting conductance was 2.4 ± 0.2 M Ω^{-1}, mean ± s.e. mean ($n = 12$). The application of GABA in concentrations greater than 3 μM was followed by a hyperpolarizing potential and an increase in input conductance. These effects were reversible and dose-dependant. Conductance log dose-response relationships were obtained from 6 preparations. The dose-response relationships were described by a form of the Hill equation (1), where Δg is the conductance

change produced by the concentration of GABA, A.

$$\Delta g = \frac{\Delta g_{max}}{1 + \left(\frac{K_{\frac{1}{2}}}{A}\right)^{n_H}} \quad (1)$$

$K_{\frac{1}{2}}$ is the concentration of GABA producing the half maximum conductance change, Δg_{max} is the maximum conductance change, and n_H is the Hill coefficient. A least squares estimate of the values of n_H, $K_{\frac{1}{2}}$ and Δg_{max} was made using an iterative procedure for each of the 6 bags. The size of the responses did not appear to depend upon the location of the bags. The mean ± s.e. mean of n_H was 3.1 ± 0.6 (n = 6). The mean ± s.e. mean of $K_{\frac{1}{2}}$ was 18 ± 3 μM (n = 6). The mean ± s.e. mean of Δg_{max} was 4.5 ± 0.9 M Ω^{-1} (n = 6).

It was also possible to estimate the reversal potentials of the GABA responses by extrapolation. The mean ± s.e. mean was 29.5 ± 2 mv (n = 7) more negative than the resting potential at 10^{-5} M GABA.

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Induction of analgesia and morphine potentiation by irreversible inhibitors of GABA-transaminase

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Attempts have been made to ascribe a role for GABA in analgesia, but the results have been controversial. For example, the GABA agonist muscimol enhances morphine analgesia (Biggio, Della Bella, Frigeni & Guidotti, 1977), whereas the GABA-transaminase inhibitor aminooxyacetic acid has been reported to antagonize morphine analgesia (Ho, Loh & Way, 1976). The recent availability of two irreversible inhibitors of GABA-transaminase, γ-vinyl GABA (GVG; DL-4-aminohex-5-enoic acid; RMI 71754) and γ-acetylenic GABA (GAG; DL-4-aminohex-5-ynoic acid; RMI 71645) led to this study of their analgesic properties, their effects upon morphine analgesia and their utilization during morphine-withdrawal to detect any change in sensitivity of the GABA system.

Analgesia was tested using groups of ten CD_1 mice (20–25 g) on a 52°C hot-plate. GVG (ED_{50} 770 (670–870) mg/kg i.p.) and GAG (ED_{50} 51 (46–56) mg/kg i.p.) were active, but at higher doses than morphine HCl (ED_{50} 6.9 (6.1–7.7) mg/kg s.c.). Analgesia was maximal 4 to 6 h after GVG or GAG (ED_{50} dose i.p.), correlating with the rise in mouse brain GABA levels (Jung *et al.*, 1977a, b). Analgesia could be demonstrated with the (+)-isomer of GVG, the form active as a GABA-transaminase inhibitor; none was detectable after the inactive (−)-isomer of GVG up to 800 mg/kg i.p. GVG and GAG-induced analgesia was not preventable by naloxone HCl (1 mg/kg), nor did these compounds inhibit (up to 10^{-4} M) the contractions of the isolated transmurally-stimulated guinea pig ileum, indicating lack of opioid involvement. In the rat, analgesia was shown using the tail-stimulation test (Hoffmeister, 1968) using groups of six male Sprague–Dawley rats (140–170 g). Although GVG (ED_{50} 1100 (960–1240) mg/kg i.p.) and GAG (ED_{50} 61 (50–72) mg/kg i.p.) were less active than morphine HCl (ED_{50} 1.60 (1.40–1.90) mg/kg s.c.), they also inhibited both vocalization and vocalization after-discharge.

The analgesic activity of morphine HCl in mice on the 56°C hot-plate was potentiated by a factor of three after GVG (800 mg/kg i.p.), with GVG itself being inactive. Lower doses of GVG did not potentiate morphine, suggesting a large increase in GABA levels (Jung *et al.*, 1977b) is necessary for this action. In rats withdrawn from morphine (60–840 mg/kg i.p. through 14 days), the hypothermia elicited by GVG (800 mg/kg i.p.) and GAG (100 mg/kg i.p.) did not differ significantly from that in controls, indicating that no change in sensitivity in the GABA system occurs during withdrawal.

It is concluded that the administration of GVG and GAG can result in analgesia, with a temporal relationship between analgesia and increased brain GABA levels. Only the GVG isomer which is active as a GABA-transaminase inhibitor has analgesic properties. There is enhancement of morphine analgesia by elevated GABA levels, although changes in sensitivity of the GABA system on morphine-withdrawal are not evident. These results support a causal relationship between increased brain GABA levels and analgesia, although the active sites remain to be explored.