their tendency to cause gastric erosions in short-term tests in rats. Wy 23205, 3[4,5-Di-*p*-chlorophenyloxazol-2-yl] propionic acid, exhibited potent anti-inflammatory activity in a variety of animal tests. Unlike conventional anti-inflammatory drugs, it showed only a very limited tendency to cause gastric erosions in rats.

Wy 23205 was twice as potent as phenylbutazone in reducing carrageenin-induced inflammation of the rat hind paw. It reduced the severity of all the inflammatory symptoms of rat adjuvant polyarthritis, its potency being slightly less than that of indomethacin and 8–20 times that of phenylbutazone. Daily oral doses of 2 to 30 mg/kg exhibited significant anti-inflammatory activity and were well tolerated by rats suffering from polyarthritis, whereas doses of indomethacin above (10 mg/kg)/day were lethal. At doses within the ranges used to demonstrate the anti-inflammatory activity aspirin, phenylbutazone and indomethacin all caused bleeding and gastric erosions, the severity of which was maximal 12 h after the drugs were administered. With Wy 23205, on the other hand, even after doses considerably in excess of those necessary for the maximal anti-inflammatory effect, no dose-related gastric damage was elicited (Fig. 1).

In anaesthetized guinea-pigs, Wy 23205 was more potent than any other drug in suppressing the reduction of thoracic compliance caused by bradykinin. An intravenous dose of 100 μg/kg Wy 23205 completely blocked the response to 16 μg bradykinin, intravenously. Like other anti-inflammatory drugs, however, Wy 23205 did not antagonize the actions of bradykinin, histamine, 5-hydroxytryptamine or acetylcholine on the guinea-pig isolated ileum.

Thus, the pharmacological profile of Wy 23205 is that of a potent non-steroidal anti-inflammatory agent which is relatively free from gastric irritant side-effects.

Evidence that bicuculline can both potentiate and antagonize GABA

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Curtis, Duggan, Felix & Johnston (1970a, b) have shown that the convulsant alkaloid bicuculline can antagonize the depressant effects of iontophoretically applied γ-aminobutyric acid (GABA) on mammalian central neurones. Godfraind, Krnjević & Pumain (1970), however, were not able to antagonize GABA consistently with bicuculline on cortical neurones.

We, also, have found that bicuculline can antagonize GABA on cortical neurones but, additionally, have observed potentiation in some cases. In our experiments, extracellular action potentials from feline cortical neurones, firing spontaneously or driven by glutamate or (±)-homocysteic acid, were recorded via a glass micropipette and counted on an interval-time spike counter (ITSC) and also displayed on a rate-meter trace. The firing rate of all cells was depressed by iontophoretically applied GABA. The percentage inhibition of firing (calculated from the ITSC data) at successive 5 or 10 s intervals during an application of GABA was plotted against the cumulative amount of GABA applied (expressed as coulombs of charge passed by the GABA barrel). From the dose-response curves so obtained, the coulombs of GABA required to cause 50% inhibition of firing were determined. Using these estimates, the cell's response to GABA was compared before, during and after the iontophoretic application of bicuculline (50–150 nA).

In some cells, bicuculline clearly antagonized GABA causing either a parallel shift of the dose-response curve to the right or sometimes a depression of the maximum. In other cells, potentiation was seen in the form of a shift to the left of the dose-response curve. Occasionally, both potentiation and antagonism were seen sequentially in the same cell or even within a single dose-response curve when the lower part of the curve was shifted to the left and the maximum was depressed. In all cases, the responses to GABA following termination of the bicuculline application returned rapidly towards control values. In fifty-one out of sixty cells tested, there was either a change in the response of the cell to GABA or a change in the firing rate of the cell in the presence of bicuculline. This indicates that bicuculline was reaching these cells. The responses to GABA were potentiated by bicuculline in twenty cells and antagonized in thirty-one cells. Most of these changes were small, however, being greater than 2-fold in only seven cases of antagonism and nine cases of potentiation.

These results suggest that bicuculline is not a simple GABA antagonist and should be used with caution in the identification of GABA-mimetic compounds or GABA-mediated synapses in the central nervous system.

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Effect of atropine on acetylcholine release from cerebral cortical slices stimulated at different frequencies

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Atropine increases the release of acetylcholine (ACh) from the cerebral cortex *in vivo* (Mitchell, 1963). To determine the effect of atropine on the ACh release mechanism more directly, slabs of rat cortex (300–400 mg) were sliced into strips (0·2 mm thick) and were perfused *in vitro* according to Srinivasan, Neal & Mitchell (1969) with oxygenated Krebs solution containing 2×10^{-4} M eserine and 10^{-5} M choline. After perfusion for 1 h, samples were collected every 2·5 min and their ACh content was assayed on the leech muscle. After four control samples square wave pulses of alternating polarity (5 ms duration, 40 mA) were applied at frequencies of 0·25, 1, 4, 16 and 64/second. The release of ACh remained constant during 40 min of continuous stimulation except at the highest frequency used. Without drugs added to the Krebs solution the minute output rose and the output per volley slowly declined as the frequency of stimulation increased (Fig. 1). In the presence of 3×10^{-7} M atropine the unstimulated output was not any higher than without atropine ((18·4$\pm$1·2 ng/g)/min without atropine, (17·1$\pm$1·7 ng/g)/min with atropine), but atropine greatly enhanced the ACh release evoked by stimulation, especially at low frequencies (Fig. 1). Addition of 3×10^{-7} M atropine or atropine methylnitrate to the perfusion fluid during stimulation immediately increased ACh release.