It has been suggested that the antagonism of imipramine-like drugs towards hypothermia produced by apomorphine depends on their noradrenaline-like activity (Maj et al 1974; Schelkunov 1977; Puech et al 1978). Among the antidepressants we examined, nomifensine (see above) and femoxetine exhibited such an activity; femoxetine, besides its strong action on 5-HT neurons, is a weak inhibitor of the NA uptake (Buus Lassen et al 1975). Both drugs, femoxetine at the highest dose, antagonize apomorphine-induced hypothermia. But paroxetine, which we found to be a much stronger antagonist than femoxetine, has been reported to have no effect on the NA uptake (Buus Lassen 1978). Of the drugs which were ineffective in counteracting the apomorphine-induced hypothermia, only mianserin increased the availability of NA in the synaptic cleft as a result of the presynaptic receptor blockade and uptake inhibition, though a functional significance of this effect seems doubtful in view of a concurrent blockade of postsynaptic NA receptors (Baumann & Maitre 1977).

However, irrespective of the mechanism of antagonistic action of imipramine-like drugs and some other antidepressants, apomorphine-induced hypothermia would seem to have disadvantages for studying putative antidepressant drugs in animals.

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Gastric relaxation by apomorphine and ATP in the conscious dog

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The non-adrenergic, non-cholinergic inhibitory vagal system which is involved in the receptive relaxation of the stomach during food intake in cat, dog and man (Abrahamsson & Jansson 1969; Jahnberg 1977), mediates the gastric relaxation produced by apomorphine in the cat (Abrahamsson et al 1973). In the dog apomorphine induces a gastric relaxation (Lefebvre & Willems 1978) which is probably also mediated by the non-adrenergic, non-cholinergic vagal system: indeed, apomorphine acts in the dog as in the cat via the chemoreceptor trigger zone (Wang & Borison 1952).

ATP or a related nucleotide has been proposed as the peripheral neurotransmitter of the non-adrenergic, non-cholinergic vagal system (Burnstock et al 1970; Burnstock 1972). We have tested the purinergic hypothesis in the conscious dog by studying the influence of theophylline, a selective antagonist of the inhibitory effects of adenosine or adenine nucleotides on gastrointestinal preparations (Okwuasaba et al 1977; Ally & Nakatsu 1976), on the gastric relaxation produced by apomorphine and by ATP. We have also examined the influence of domperidone, an anti-emetic dopamine antagonist (Reyntjens et al 1978), which has been shown to block the apomorphine-induced gastric relaxation in the anaesthetized dog when administered intracisternally (Lefebvre & Willems 1978).

In female mongrel dogs a gastric fistula was obtained by placing a Thomas cannula in the ventral wall of the stomach. The animals were allowed to recover from surgery for three weeks. They were deprived of food 20–24 h before each experimental session but had free access to water. Intragastric pressure was monitored in the standing position by introducing, through the cannula, a balloon which was connected through a fluid-filled tube to a Statham pressure transducer. The balloon was filled with 500 ml of water at 37 °C, introducing 125 ml each 5 min (Valenzuela 1976). Three dogs were used; in each 6 experiments with ATP and 6

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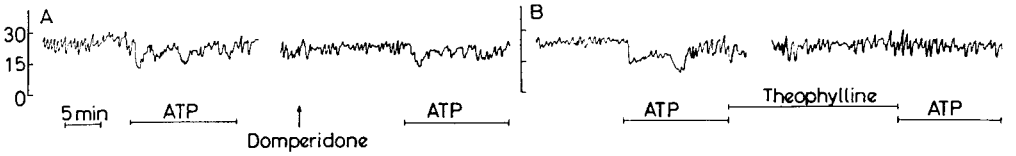

FIG. 1. Influence on gastric pressure by intravenous ATP (0·8 mg kg^{-1} min^{-1}): A, before and after domperidone (1 mg kg^{-1} i.v.); B, before and after theophylline (5 mg kg^{-1} i.v.). Both experiments were performed in the same dog. Ordinate: gastric pressure (cm H_2O).

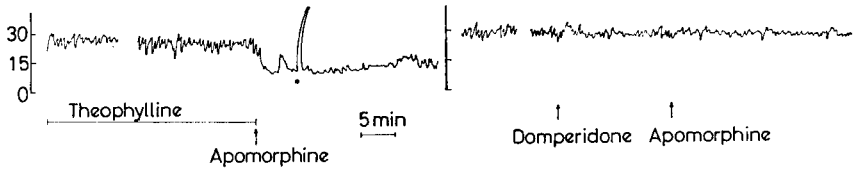

FIG. 2. Influence on gastric pressure by subcutaneous apomorphine (0·03 mg kg^{-1}): A, after theophylline (10 mg kg^{-1} i.v.); B, after domperidone (1 mg kg^{-1} i.v.). Both experiments were performed in the same dog. ●: vomiting. Ordinate: gastric pressure (cm H_2O).

experiments with apomorphine were performed (in both cases 2 for theophylline, 2 for domperidone and 2 for the domperidone solvent [acetic acid in water for injection]).

In the ATP experiments (Fig. 1), ATP (0·8 mg kg^{-1} min^{-1}) was infused over 15 min, and the ATP infusion was repeated after 30 min. In between, theophylline (5 mg kg^{-1} i.v. over 30 min), domperidone (1 mg kg^{-1} i.v. bolus 15 min before the second ATP infusion) or the domperidone solvent (0·2 ml kg^{-1} i.v. bolus 15 min before the second ATP infusion) was given. In preliminary experiments, it was found that this dose of ATP was needed to obtain a consistent fall in gastric tone.

In all experiments (n = 18), the first ATP administration produced a rapid gastric relaxation, reaching a maximum within 5 min after the start of the ATP infusion but recuperating before it ended. During the second ATP infusion, the gastric relaxation was completely prevented by theophylline (n = 6), but not by domperidone (n = 6) or its solvent (n = 6). Two representative experiments are shown in Fig. 1.

The apomorphine experiments (Fig. 2) started with an infusion of theophylline (10 mg kg^{-1} i.v. over 30 min), an injection of domperidone (1 mg kg^{-1} i.v.) or an injection of the domperidone solvent (0·2 ml kg^{-1} i.v.). Apomorphine (0·03 mg kg^{-1}) was then injected subcutaneously at the end of the theophylline infusion or 15 min after the injection of domperidone or its solvent. This dose of apomorphine was the smallest found in preliminary experiments to produce a gastric relaxation consistently.

In the experiments where first the domperidone solvent (n = 6) or theophylline (n = 6) was given, gastric relaxation was observed within 8 min after the injection of apomorphine. In 10 of these 12 experiments the gastric relaxation was followed by vomiting. Domperidone completely prevented the apomorphine effects (n = 6). Two representative experiments are shown in Fig. 2.

Adenosine and related nucleotides produce a relaxation in several gastrointestinal smooth muscle preparations. In this study, ATP elicited a gastric relaxation in the conscious dog. This ATP effect was blocked by theophylline, which is in agreement with the theophylline antagonism of ATP-induced gastrointestinal relaxations observed by others (Okwuasaba et al 1977; Ally & Nakatsu 1976). Apomorphine also produced a gastric relaxation, which was completely blocked by domperidone. This confirms our previous findings in the anaesthetized animal: in this study, the effect of domperidone was more pronounced, but the dose and the route of administration of apomorphine was different from that in our previous study (Lefebvre & Willems 1978). Theophylline, even in a dose twice as high as the dose that antagonized the ATP effect, did not prevent the apomorphine-induced gastric relaxation. If we assume that in the dog, the apomorphine-induced gastric relaxation is mediated via the chemoreceptor trigger zone and the activation of the non-cholinergic, non-adrenergic vagal inhibitory system, our results do not support the purinergic hypothesis for this inhibitory vagal system.

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Effects of hydrocortisone on binding of IgG or C3b-coated erythrocytes to human monocytes and polymorphonuclear leucocytes

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Over the past decade, studies in many laboratories have suggested that anti-inflammatory steroids are capable of inhibiting each of the steps in the phagocyte-foreign body interaction, thereby rendering the host more susceptible to aggression by microorganisms (Katler & Weissmann 1977). These results, if extended and confirmed, would adequately account for the increased incidence of infection in patients treated with steroids for long periods of time. However, in most studies steroid concentrations were higher than those used therapeutically, thus making it difficult to evaluate the pharmacological relevance of the experimental findings. Furthermore, conflicting results have been obtained probably because of differences in test systems, time of incubation or steroid dosage. Thus, while Rinehart et al (1974) have claimed that corticosteroids have no effect on binding of IgG or C3b-coated erythrocytes to human monocytes, Schreiber et al (1975) have reported that several steroids, including hydrocortisone, inhibit monocyte receptor activity for both IgG and C3b in a dose-response fashion. We have therefore re-examined the effects of hydrocortisone on monocyte receptor activity and have extended the investigation to include polymorphonuclear leucocytes.

Monocytes and polymorphonuclear leucocytes (PMN) were isolated from human peripheral blood according to Ehlenberger & Nussenzweig (1977). Isolated monocytes were resuspended in 3 ml of medium (RPMI 1640 with added 10 mM Hepes, pH 7·4; GIBCO) containing 15% autologous serum. 100-μl aliquots of this suspension (1×10^6 cells ml^{-1}) were layered on glass cover slips (10×10 mm) and these were incubated for 30 min at 37 °C under a 5% CO_2 atmosphere. Non adherent cells and serum were decanted and the adherent cells were washed four times with medium, incubated for 30 min at 37 °C in fresh medium and washed once more before being used in the binding assays. Monolayers were more than 95% mononuclear, and 99% of these cells were viable. Isolated PMN were resuspended in plasma (1×10^8 cells ml^{-1}) and 200 μl aliquots of the suspension were layered on cover glasses (18×18 mm) and incubated for 20 min as above. Monolayers were washed gently by dipping the cover slips in three successive beakers of fresh medium, and then incubated (30 min at 37 °C) in Petri dishes filled with medium supplemented with 15% foetal calf serum. They were rinsed in medium once more before use in binding assays. Monolayers were usually 90% polymorphonuclear, and 97% or more of these cells were viable. Sheep red blood cells (E) in Alsever's solution (10^9 cells ml^{-1}) were ^{51}Cr-labelled (Tolone 1968) and sensitized with an appropriate dilution of rabbit IgM anti-E (Cordis). After washing, IgM-sensitized cells (EA) were coated with C3b via sequential addition of purified C1, C4, C2 and C3 (Cordis). Coated cells were washed in medium containing 10 mM Na_3HEDTA to remove C1, and incubated at 37 °C for 2 h to decay C2. These cells are referred to as EAC3b although they also contain C4b. Aliquots of either EA or EAC3b were coated with IgG by incubating (30 min at 37 °C) 1 ml volumes of each preparation (10^9 cells) with equal volumes of medium containing an appropriate dilution of rabbit IgG anti-E (Cordis). These cells are referred to as EAIgG and EAC3bIgG respectively. The number of C3b or IgG molecules bound per E (800 and 400 respectively) was determined by C1 fixation and transfer (Schreiber et al 1975). Binding assays were performed by overlaying cover slips (each containing about 5×10^4 phagocytes) with $1{\cdot}25 \times 10^7$ opsonized E in 0·25 ml of medium supplemented (or not) with hydrocortisone 21-sodium succinate (Sigma) at the indicated concentrations, incubating 45–60 min at 37 °C, decanting unbound E and washing five times with fresh medium. Phagocyte monolayers were then lysed with H_2O and the lysate was assayed for radioactivity in a gamma counter. All experiments were in triplicate.

Under our experimental conditions, where a large excess of erythrocytes is allowed to settle on the phagocyte monolayers thereby providing a saturating cell density and absence of shear forces between erythrocytes and phagocytes, both monocytes and PMN-leucocytes bind effectively to IgG or C3b-coated sheep red blood cells (Table 1). This binding is markedly

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