Conclusions

In the present study antipyrine has shown a fast drug release from tablets and rapid and reproducible absorption. Its analgesic efficacy is at least as good as that of aspirin and acetaminophen. Moreover, it seems that antipyrine shows an earlier onset of action than aspirin and a longer duration of action than acetaminophen. However, this comparison was only performed at a dose of 1 g of the three drugs. Although this dose is within the recommended dose range for acute pain treatment, more information is needed on the dose response curve for antipyrine as well as acetaminophen and aspirin.

As reports on serious side effects are rare, one should reconsider antipyrine as a useful alternative to the over-the-counter analgesics aspirin and acetaminophen. We propose additional clinical trials to obtain further information on the therapeutic value of antipyrine. The present study reconfirms the significance of evoked potential monitoring as a non-invasive tool to follow pharmacodyamics. The particular advantage of this method compared with traditional subjective methods is the fact, that a smaller number of subjects is needed to show differences between different kinds of drug treatment with statistical significance. In general, quantitative electroencephalography represents a valuable method in comparative drug efficacy studies by providing detailed information on the time course of action for drugs with effects on the nervous system.

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REPORTS

Prostaglandin E_1-induced Catalepsy in the Rat: Role of Putative Neurotransmitters

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Abstract: Prostaglandin E_1 (PGE_1) produced dose-related catalepsy in rats when administered intracerebroventricularly. PGE_1-induced catalepsy was significantly inhibited after pretreatment with pharmacological agents known to attenuate central serotonergic and cholinergic activity. It was also inhibited by $PGF_{2\alpha}$ and naloxone. On the contrary, treatments enhancing central dopaminergic activity also reduced the cataleptic effect of PGE_1. The results suggest that PGE_1 induces catalepsy in rats by modulating activity of central neurotransmitters.

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Prostaglandins (PGs), particularly of the E series, have been reported to induce catalepsy, defined as inability to correct externally imposed postures, in several species including rats, both on peripheral (1) and central administration (2). PGE_1 is known to potentiate morphine (3) and cannabis induced catalepsies in rats, whereas $PGF_{2\alpha}$ and PG synthesis inhibitors attenuate the same (3, 4). Furthermore, PG synthesis inhibitors have been reported to reduce restraint stress induced potentiation of cannabis (5) and haloperidol (6) induced cataleptic responses in rats. This form of experimental stress is known to enhance rat brain PG activity (7). PGs are now thought to function as modulators of central monoaminergic (8, 9) and cholinergic (10) neurotransmission. The present study was undertaken to assess the role of central neurotransmitters in the cataleptic effect of centrally administered PGE_1.

Materials and Methods

Wistar strain albino rats (150–200 g), of either sex, were used. They were housed in individual perspex cages with free access to food (hind lever rat diet) and water, at ambient temperature of 22–25°C. Food was withdrawn 18 h prior to and water just before experimentation.

Catalepsy was initially assessed by a staging system (11). Quantification of catalepsy was done by the "ring test" (12), where the rat was placed on a steel ring, 12 cm in diameter, fixed to a steel stand at a height of 35 cm. The time during which the rat remained motion-

less, with complete cessation of snout and whisker movements, out of a total observation period of 5 min, was converted into "per cent immobility".

Graded doses of PGE_1 were administered intracerebroventricularly (icv) through indwelling cannulae inserted into the right lateral ventricle stereotaxically. Catalepsy was assessed after 15 min of PGE_1 administration. No attempt was made to investigate the duration of catalepsy.

The following drugs, with dose and pretreatment time given in parenthesis, were used to investigate the mechanism of PGE_1 induced catalepsy: 5,6-dihydroxytryptamine (DHT, 75 μg/rat, 48 h), *p*-chlorophenylalanine (PCPA, 100 mg/kg, once daily for 3 d), hemicholinium (20 μg/rat, 45 min), atropine sulphate (5 mg/kg, 1 h), diclofenac sodium (25 mg/kg, 6 h), *l*-dopa (100 mg/kg, 30 min) + benserazide (50 mg/kg, 30 min) with or without diethyl dithiocarbamate sodium (300 mg/kg, 3 h), amantadine (25 mg/kg, 30 min), $PGF_{2\alpha}$ (20 μg/rat, 15 min) and naloxone (1 mg/kg, 30 min). All the drugs were dissolved or suspended in normal saline and injected i.p., except DHT, hemicholinium and $PGF_{2\alpha}$, which were dissolved in artificial cerebrospinal fluid (volume 10 μl) and administered icv. The doses mentioned refer to the respective salts. The doses of the drugs used are based on earlier work from this laboratory, and none of them showed any cataleptic effect *per se* in the doses used (3–6).

Results and Discussion

PGE_1 (5, 10 and 20 μg/rat, icv) produced a dose-related cataleptic behavior, as assessed 15 min after its administration. Since the last dose (20 μg/rat) produced a sub-maximal effect, this dose was used for further studies. PGE_1 catalepsy was significantly attenuated after pretreatment with DHT, PCPA, hemicholinium, atropine, amantadine, $PGF_{2\alpha}$ and naloxone. *l*-Dopa, administered in conjunction with benserazide, also produced inhibition of PGE_1 catalepsy; however, the inhibition was more marked when diethyl dithiocarbamate (DDC) was added to the regimen. The data are summarized in Table 1.

PGE_1 has been earlier reported to induce catalepsy in several animal species, including rats, both on peripheral (1) and central (2) administration. PG synthesis inhibitors are known to inhibit the cataleptic effects of morphine (3) and cannabis (4), as well as to attenuate restraint stress induced potentiation of cannabis (5) and haloperidol (6) induced catalepsies. Restraint stress has been reported to enhance rat brain levels of PGs (7).

PGE_1 induced catalepsy was significantly inhibited by DHT, a selective serotonergic neuronolytic agent (13), and by PCPA, a serotonin synthesis inhibitor (14), suggesting that reduction in central serotonergic activity attenuates the behavior. A role for serotonin has been envisaged in neuroleptic catalepsy in rats (15). Recent studies from this laboratory suggest a modulatory role for PGs in central serotonergic neurotransmission in rats (8). PGE_1 has been shown to enhance turnover of serotonin (16), whereas $PGF_{2\alpha}$ was reported to decrease it (17). PG synthesis inhibitors were found to decrease rat brain levels of serotonin (18) and to reduce morphine (18), cannabis and restraint stress (19) induced increase of the monoamine. Since $PGF_{2\alpha}$ was found to inhibit PGE_1 catalepsy, it is likely that the antagonism is related to the decrease of central serotonergic activity by the former in this species. It is of interest to note that several serotonin-mediated central actions of PGE_1 have been reported to be mitigated by $PGF_{2\alpha}$ (20).

The inhibition of PGE_1 catalepsy by hemicholinium, which inhibits synthesis of acetylcholine, and atropine, a muscarinic cholinolytic agent, indicates that decrease in cholinergic activity attenuates the behavior. PGs of the E series have been reported to enhance rat brain concentrations of acetylcholine (10). Naloxone, a specific antagonist of endogenous opioid receptors, markedly antagonized PGE_1 catalepsy. β-Endorphins are known to induce catalepsy in rats (21), and naloxone has been reported to reduce the increase of rat brain PGs induced by met-enkephalin (22). It is, therefore, likely that PGs may be involved, at least partly, in endogenous opioid induced catalepsy, or vice-versa.

l-Dopa, administered with a peripheral decarboxylase inhibitor benserazide, reduced PGE_1 catalepsy. However, the attenuation was much more marked when DDC, a dopamine-β-hydroxylase inhibitor (23), was added to the regimen. It is known that in the latter situation *l*-dopa behaves primarily as a dopamine precursor, with blockade of the biosynthetic pathway from dopamine to noradrenaline (23). The inhibitory role of dopamine in PGE_1 catalepsy is further emphasized by the attenuating effect of amantadine, a dopamine receptor agonist, on this behavior. The findings are in conformity with the reported dopamine deficiency hypothesis of catalepsy (24). PGs of the E series are known to inhibit the release of catecholamines from central dop-

Table I. Effects of Some Drugs, Influencing Central Neurotransmitter Activity, on PGE_1-Induced Catalepsy in Rats

Groups	n	Percent Immobility Mean ± S.E.	P[c]
Control (artificial CSF)	10	10.5 ± 3.2	–
PGE_1 (5 μg)	10	18.6 ± 5.9	n.s.[a]
PGE_1 (10 μg)	10	46.9 ± 3.4	< 0.001[a]
PGE_1 (20 μg)	10	71.8 ± 2.9	< 0.001[a]
DHT + PGE_1 (20 μg)	6	42.3 ± 4.8	< 0.001[b]
PCPA + PGE_1 (20 μg)	8	51.4 ± 3.9	< 0.001[b]
Hemicholinium + PGE_1 (20 μg)	8	54.6 ± 3.7	< 0.01[b]
Atropine + PGE_1 (20 μg)	8	59.5 ± 2.9	< 0.01[b]
Diclofenac + PGE_1 (20 μg)	6	74.0 ± 2.7	n.s.[b]
PGF_{2a} + PGE_1 (20 μg)	6	56.1 ± 4.2	< 0.01[b]
Naloxone + PGE_1 (20 μg)	8	46.2 ± 5.2	< 0.01[b]
l-Dopa + Benserazide + PGE_1 (20 μg)	8	58.4 ± 5.0	< 0.01[b]
l-Dopa + Benserazide + DDC + PGE_1 (20 μg)	8	39.0 ± 5.9	< 0.001[b]
Amantadine + PGE_1 (20 μg)	8	44.5 ± 3.6	< 0.001[b]

[a] Statistical significance in comparison to Control group
[b] Statistical significance in comparison to PGE_1 (20 μg) group
n.s. indicates statistical non-significance ($P > 0.05$)
[c] Student's t-test used for statistical analysis of data

aminergic and noradrenergic neurones (9).

An interaction between cholinergic and dopaminergic neurotransmitter systems has been postulated as the mechanism of neuroleptic catalepsy (24). Dopaminergic inputs on striatal cholinergic neurones and cholinergic inhibitory effects on striatal dopaminergic cell bodies have been established (25). A similar inverse relationship between striatal serotonergic and dopaminergic systems has been envisaged (25) in neuroleptic catalepsy (15). It is likely that PGE_1 exerts its cataleptic effect by modulating serotonergic, cholinergic and dopaminergic neurotransmission. Increased cholinergic and serotonergic activity, concomitant with reduced dopaminergic activity of rat brain, is reflected in the cataleptic state induced by PGE_1. The ability of $PGF_{2\alpha}$ to inhibit PGE_1 catalepsy lends credence to the hypothesis that the two PGs function in opposite directions in modulating rat brain serotonergic activity (8). The inability of diclofenac, a PG synthesis inhibitor, to affect PGE_1 catalepsy, is entirely predictable since the PG was administered exogenously.

An interesting aspect revealed in the present study relates to the inhibitory effect of naloxone on PGE_1 catalepsy. Little information exists on the possible inter-relationships between PGs and the endogenous opioid peptides, apart from isolated reports (22). Since both these groups of neuroregulators have been envisaged to act as modulators of central neurotransmission, such studies are necessary for better understanding of the complexities of synaptic transmission in the central nervous system.

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Morphine Inhibition of Theophylline Clearance

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Abstract: The effects of morphine on the single dose pharmacokinetics of theophylline were examined in two groups (6 rats/group) of male Sprague-Dawley rats after the administration of theophylline (6.25 mg/kg) alone and in conjunction with a 5 mg /kg I.V. dose of morphine sulfate. Concomitant morphine administration resulted in a 55 % reduction in theophylline clearance (0.14 ± 0.04 vs. $0.31 \pm 0.061 \cdot h^{-1} kg^{-1}$; $p < 0.0005$). The reduction in theophylline clearance with morphine administration was accompanied by a significant prolongation in theophylline half-life (3.5 ± 1.5 vs. 1.4 ± 0.35 h; $p < 0.02$). No changes in the volume of distribution of theophylline occurred with co-administration of morphine. The mechanism of this pharmacokinetic interaction may be partially related to competition between theophylline and morphine for enzymes which metabolize these compounds.

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Intravenous morphine and aminophylline have been widely used together in the treatment of acute pulmonary edema. Piafsky et al. (1) have examined the disposition of theophylline in nine patients with acute cardiogenic pulmonary edema (five of whom received morphine) and have noted a 33 % decrease in the systemic clearance of theophylline. Potential causes for this reduced clearance of theophylline include hypoxemia, hepatic congestion, or a drug interaction between theophylline and other drugs which were co-administered.

The existence of a common metabolic pathway for both morphine and theophylline suggests the potential for a drug-drug interaction. Both of these drugs are partially metabolized by *N*-demethylation pathways in the liver. Competition of morphine and theophylline for drug metabolizing enzymes