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CENTRAL AND PERIPHERAL ANTIALGESIC ACTION OF ASPIRIN-LIKE DRUGS

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The peripheral and central effects of some non-steroid anti-inflammatory drugs, aspirin, indomethacin, paracetamol and phenacetin were studied by comparing their intraplantar and intracerebroventricular effects on hyperalgesia induced by carrageenin injected into the rat paw. Hyperalgesia was measured by a modification of the Randall—Selitto test. The agents tested had antialgesic effects when given by any route. Their intraventricular administration enhanced the antialgesic effect of anti-inflammatory drugs administered into the paw. Previous treatment of one paw with carrageenin reduced the oedema caused by a second injection of carrageenin in the contralateral paw. In contrast, it had no effect on the intensity of hyperalgesia but shortened the time necessary for it to reach a plateau. Administration of a prostaglandin antagonist (SC-19220) in the cerebral ventricles, in the rat paw or in both sites, significantly inhibited the hyperalgesia evoked by carrageenin. The maximal hyperalgesic effect of intraplantar injections of prostaglandin E_2 could be further enhanced by its cerebroventricular administration. It was suggested that carrageenin hyperalgesia has a peripheral and a central component and that the cyclo-oxygenase inhibitors used may exert an antialgesic effect by preventing the hyperalgesia induced by a peripheral and/or central release of prostaglandins.

Inhibition of inflammatory hyperalgesia Prostaglandin-induced hyperalgesia Antialgesia
Aspirin-like drugs

1. Introduction

Lim's classic demonstration of the peripheral site of action of non-steroid anti-inflammatory agents (Lim et al., 1964) has been reinforced by the recent finding that prostaglandins, at concentrations found in inflammatory exudates, sensitized pain receptors to mechanical or chemical stimulation (Ferreira, 1972; Rosenthale et al., 1972, Ferreira et al., 1973; Willis and Cornelsen, 1973; Juan and Lembeck, 1974; Moncada et al., 1975). It has been suggested that the analgesic effects of non-steroid anti-inflammatory agents were due to a blockade of the local synthesis of a prostaglandin induced by the inflammatory stimuli, thus preventing the development of hyperalgesia (Ferreira, 1972).

However, a central effect of non-steroid anti-inflammatory drugs is also generally accepted (Woodbury and Fingl, 1975). The action of agents such as paracetamol, phenacetin or dipyrone, which display antipyretic and antialgesic effects without conspicuous action on local oedema and erythema, is taken as an argument in favour of a central effect. How these agents act centrally has not yet been established, but it is known that they selectively inhibit nervous tissue cyclo-oxygenase with little effect on enzymatic preparations from other tissues (Flower and Vane, 1972; Dembinska-Kiec et al., 1976). Inhibition of prostaglandin release in the CNS is thought to be the mechanism responsible for the antipyretic effect of these agents (Feldberg, 1974).

In the experiments described here, the central and peripheral effects of some non-steroid anti-inflammatory drugs were studied by comparing their local and intracerebroven-

tricular effects on the hyperalgesia induced by carrageenin injected into the rat paw. The involvement of prostaglandin in the development of hyperalgesia was evaluated with a prostaglandin antagonist (SC-19220) as well as by the ability of prostaglandin E_2 to cause hyperalgesia when injected locally and/or centrally. A preliminary report of this work was presented at the Prostaglandin Symposium during the Sixth Congress of the Polish Pharmacological Society, in September, 1977.

2. Materials and methods

2.1. Animals

Male Wistar rats weighing 130—230 g were used; the number of animals is indicated for each experiment.

2.2. Hyperalgesia

A modification of the Randall—Selitto method (1957), in which constant pressure rather than increasing pressure was applied to the rat's paw, was used. The apparatus used is described in fig. 1. The pressure was discontinued (reaction time) when the animals presented a reaction characterized by a diminution of escape movements (the animal usually tries to escape from the position imposed by the experimental situation) closely followed by a change in respiratory frequency and the appearance of a typical shivering reaction (successive waves of muscular tremor). This typical reaction can be observed in the rat 10 sec after the insertion of a fine hypodermic needle in one of its hind paws. The intensity of hyperalgesia was evaluated by the change in reaction time (Δ reaction time) calculated by subtracting the value observed after carrageenin or saline injection from the reaction time before any injection (0 time). When not specified, the intensity of hyperalgesia was calculated by subtracting the values obtained 4 h after carrageenin or saline injection from the 0 time value.

All measurements were made by the same trained experimenter who was unaware of the drug being tested.

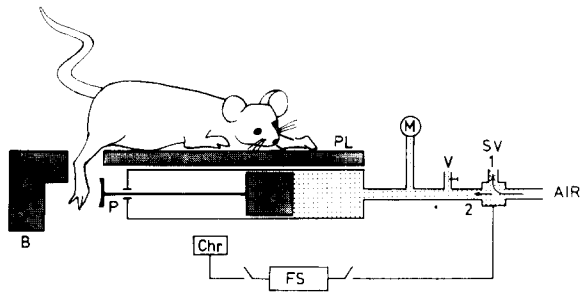

Fig. 1. Diagram of the apparatus used for measuring hyperalgesia. The rat was held against the platform (PL) and its paw positioned between the platform and the bar (B). Pressurized air was constantly introduced into the system but the solenoid valve (SV) normally let it flow out (direction 1). A foot switch (FS) simultaneously activated an electric chronometer (Chr) and the solenoid valve (SV) which controls the air flow into a teflon syringe (direction 2). The increase in pressure in the system pushes the piston (P) against the paw. The final pressure reached inside the system (indicated by the manometer, M) was set at the desired value by the escape valve V.

2.3. Oedema measurement

The increase in the rat paw volume was measured by the time necessary to replace the volume of fluid displaced by immersion of the rat paw up to the tibiotarsic articulation. The paw was immersed in a cuvette which was continuously refilled with fluid (saline—lauryl sulphate, 2 mg/ml) at a constant rate of 2 ml/min by means of an infusion pump thus allowing conversion of time (sec) to volume (μl). The increase in volume (Δ volume) of the inflamed paw was obtained by subtracting the volume measured before carrageenin administration from the observed value.

2.4. Administration routes

2.4.1. Intracerebroventricular injections (i.c.v.)

I.c.v. injections were made according to a modification of the technique described by Corrêa and Graeff (1974). The rat was anaesthesized with ether and its head was held horizontally by a stereotaxic appartus (David

Kopf 900). The calvarium was exposed and a trephine hole of 1 mm diameter was drilled 1.8 mm lateral to the coronary and 1.5 mm posterior to the sagittal suture. A cannula (0.7 mm outside diameter) connected to a Hamilton syringe (RN-705, 50 µl) by polyethylene tubing (PE-50) was introduced 3.2 mm deep into the brain by means of the electrode carrier. The correct placement of the cannula was indicated by the absence of backflow when 10 µl of fluid was injected. Injections were made over a period of 10 sec. The entire surgical and injection procedure lasted less than 5 min.

2.4.2. Intraperitoneal injections (i.p.)

I.p. injections of non-steroid anti-inflammatory drugs were given 2 h after the intraplantar injection of carrageenin. The volume did not exceed 0.5 ml and doses are indicated for each experiment.

2.4.3. Intraplantar injections (i.pl.)

The volume of i.pl. injections was 0.1 ml. The dose for carrageenin was 100 µg. For non-steroid anti-inflammatory agents or PGE_2 the doses indicated in each experiment.

2.5. Drugs and solvents

Carrageenin (Viscarin, Marine Colloids, USA), morphine hydrochloride (Merck, AG), pentobarbital sodium (Nembutal, Abbot, USA), chlorpromazine (Rhodia) and SC-19220 (Searle, USA) were dissolved in saline. PGE_2 (Upjohn, USA), phenacetin (Sigma, USA), paracetamol (Sigma, USA) were dissolved in ethanol and diluted with saline (1/10). Paracetamol and phenacetin at 400 µg/ml gave a fine homogeneous suspension. Indomethacin (Merck, AG) and aspirin (USP) were dissolved in Tris buffer 0.1 M, pH 7.8. All drugs were dissolved just before utilization. In all experiments an equal volume of vehicle was used as control for the i.c.v., i.pl. or i.p. injections. If the drugs were initially dissolved in ethanol or Tris these agents were also incorporated into the saline control.

2.6. Statistical analysis

The data were analysed by means of Student's *t*-test and significance was set at $P < 0.05$.

3. Results

3.1. Choice of rat paw compressing pressure

Instead of applying increasing pressure to the rat paw as described by Randall—Selitto (1957), a constant pressure was selected on the basis of the results in fig. 2. The left panel shows that the rats responded faster when compression was applied to inflamed paws. The greatest difference in reaction time (saline minus carrageenin reaction time) was observed at a pressure of 20 mm Hg. This pressure was used in all experiments.

3.2. Influence of drugs on control paws

Fig. 2, right panel shows that paws injected with saline showed no significant difference from zero time measurements. Non-steroid anti-inflammatory agents such as indomethacin affected the intensity of hyperalgesia of inflamed paws (see also table 1) but had no effect on saline-injected paws (see also table 2). A centrally acting analgesic like morphine increased the response time of saline- and of carrageenin-injected paws equally, resulting in a negative change in Δ reaction time (right panel of fig. 2). Chlorpromazine (3 mg/kg i.p.) or nembutal (10 mg/kg i.p.) given 2 h after the carrageenin injection also diminished general motor activity and increased the reaction time of both inflamed and control paws equally so that when the value for the control paws was subtracted from the values for the inflamed paws, no significant effect on the intensity of the hyperalgesia was observed ($n = 5$): control, 24 ± 0.5 sec; chlorpromazine 23 ± 0.6; nembutal 25 ± 1.0. None of the solvents used had any effect on the responses of either normal or inflamed paws. Since the

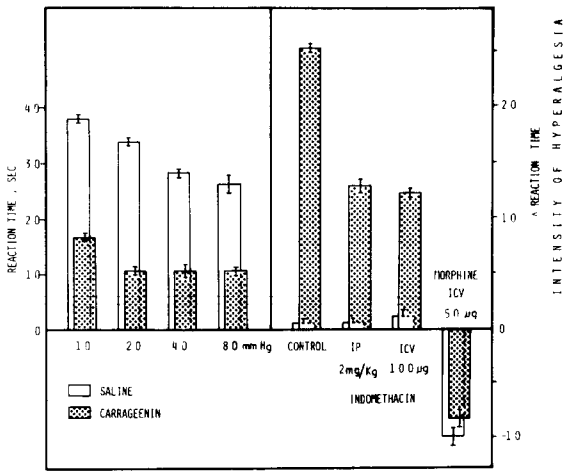

Fig. 2. Variation of reaction time in function of the compressing pressure and drugs. The left panel shows the reaction time to the various compressing pressures applied to paws injected either with carrageenin (100 µg) or saline (n = 8). The animal responded more quickly to compression of the paw inflamed by carrageenin. The right panel gives the Δ reaction time as a measure of the intensity of the hyperalgesia. This value was obtained by subtracting 0 time measurements from the reaction time found at 4th h. The results show the influence of indomethacin and morphine on the intensity of hyperalgesia. Carrageenin hyperalgesia (n = 8) was reduced by indomethacin given i.p. (n = 6) or i.c.v. (n = 5). In contrast to indomethacin, i.c.v. administration of morphine (n = 5) decreased the reaction time for inflamed as well as saline-treated paws.

TABLE 1

Effect of non-steroid anti-inflammatory drugs on carrageenin hyperalgesia.

D shows the dose of the antialgesic drugs given intraperitoneally (i.p.), into the cerebral ventricles (i.c.v.) or intraplantarly (i.p.). The controls (D = 0) received an equal volume of the vehicle used to dissolve the drugs. The intensity of hyperalgesia (Δ response time: Δ = $\overline{x}$ ± S.E.M.) induced by carrageenin was measured on the 4th h; number of animals in parentheses.

D, i.p. (mg/kg)				D, i.c.v. (µg)				D, i.pl. (µg)		
0	100	200	400	0	50	200	400	0	50	400
Aspirin										
25.0 ±0.5 [1] (7)	23.7 ±0.4 (5)	16.8 ±0.4 (5)	12.8 ±0.4 (5)	25.4 ±1.2 (5)	23.7 ±0.7 (11)	18.9 ±1.2 (5)	15.1 ±0.6 (5)	24.2 ±0.5 (12)	20.8 ±0.6 (12)	12.6 ±0.6 (6)
Paracetamol										
24.3 ±0.9 (6)	19.1 ±0.5 (6)	12.9 ±0.6 (6)	10.4 ±0.8 (6)	25.6 ±0.9 (8)	21.7 ±0.7 (16)	18.6 ±0.8 (8)	17.6 ±1.0 (8)	24.6 ±1.4 (10)	19.6 ±0.6 (13)	11.5 ±1.2 (5)
Phenacetin										
23.8 ±0.7 (6)	21.0 ±0.5 (6)	18.0 ±0.6 (6)	15.1 ±0.6 (6)	24.7 ±0.5 (6)	23.0 ±0.6 (12)	19.2 ±0.5 (6)	14.3 ±1.2 (6)	24.8 ±0.5 (10)	20.7 ±0.4 (10)	13.1 ±0.9 (5)
0	0.2	2	10	0	10	50	100	0	10	100
Indomethacin										
24.9 ±0.3 (6)	22.0 ±1.2 (6)	13.0 ±0.4 (6)	9.5 ±0.4 (6)	26.3 ±0.8 (5)	23.1 ±0.5 (10)	17.9 ±0.6 (5)	12.7 ±1.5 (5)	24.8 ±0.5 (10)	18.7 ±0.7 (10)	11.7 ±0.9 (5)

[1] Δ response time (sec).

non-steroid anti-inflammatory drugs used showed no effect on saline-treated paws, these results were omitted from some of the figures.

3.3. Effect of i.p., i.pl. and i.c.v. administration of antialgesic agents

Table 1 shows the effect of paracetamol, aspirin, phenacetin and indomethacin given i.p., i.pl. and i.c.v. A dose—response relationship for the antialgesic effect was obtained for all three routes. The maximum antialgesic effect observed did not completely restore the response to control values i.e., a Δ response time equal to zero. At the highest i.pl. doses, all four drugs matched the maximum effect obtained by the i.p. route. Although all the drugs were effective, aspirin and paracetamol appeared to be less effective when given i.c.v. than when given i.p. or i.pl. Paracetamol injected i.c.v. caused excitation of the rats; the excitation became intense with the 400 μg dose. The other agents did not produce any noticeable behavioural effect.

3.4. Effect of simultaneous i.pl. and i.c.v. injections of antialgesic agents

In this experiment the smallest effective dose of the four drugs was used for i.pl. and i.c.v. injections. Carrageenin was injected into both paws and the i.c.v. and i.pl. injections were given 2 h later and hyperalgesia was measured at the 4 th h. The animals were divided into 2 groups; one received the antialgesic drug i.c.v. and the other only the vehicle. In both groups the antialgesic drugs were injected into one paw and the vehicle into the other. This experimental design gave 4 groups: (a) vehicle i.c.v. + vehicle i.pl. = control, C; (b) vehicle i.c.v. + drug i.pl. = i.pl.; (c) drug i.c.v. + vehicle i.pl. = i.c.v.; (d) drug i.c.v. + drug i.pl. = i.c.v. + i.pl. (fig. 3). The combination of local and central administration gave an effect greater than did any of the isolated routes.

3.5. Effect of a previous i.pl. injection of carrageenin on the hyperalgesia induced by a second administration of carrageenin

The left panel in fig. 4 shows that the normal evolution of carrageenin hyperalgesia in the right paw was progressive and reached a plateau after 4 h. The lower curve shows that hyperalgesia developed faster in the left paw when the right paw had been previously

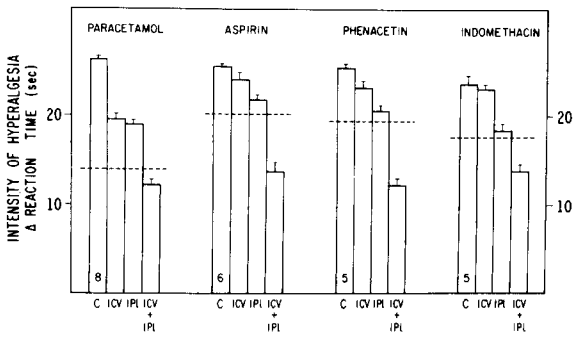

Fig. 3. Effect of combined central and local administration of antialgesics on the hyperalgesia induced by carrageenin. The doses given together or by either route were: 50 μg for paracetamol, aspirin or phenacetin and 10 μg for indomethacin. See the text for the experimental design. The summation of i.c.v. and i.pl. effects is indicated by the dotted line and the number of animals for each group is shown in the bars.

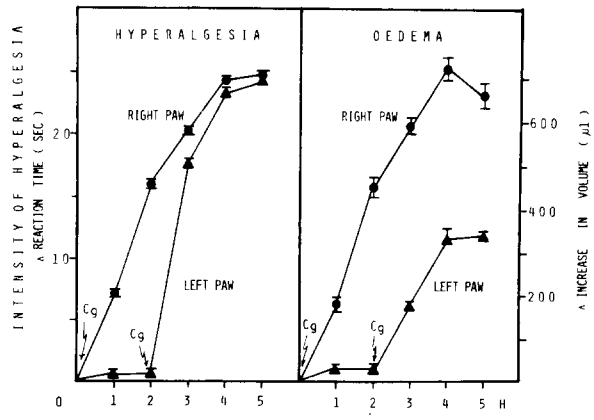

Fig. 4. Effect of a previous injection of carrageenin on the hyperalgesia and oedema induced by a second administration in the contralateral paw. The right paw (●) was injected with carrageenin (Cg) at zero time; the left paw (▲) was injected 2 h after the injection of carrageenin into the right paw. The left panel shows the evolution of hyperalgesia and the right panel the oedema (n = 6).

injected with carrageenin (2 h before). In 1 h it reached a greater value than that obtained 2 h after the first challenge. In 2 h the plateau value was reached. The right panel in fig. 4 shows that a previous injection of carrageenin in the right paw diminished the oedematogenic response to the late injection in the left paw.

3.6. Effect of i.c.v. prostaglandin injection on carrageenin-induced hyperalgesia

In this experiment two doses of prostaglandin E_2 (10 or 100 ng) were given i.c.v. half an hour after i.pl. carrageenin and hyperalgesia was measured 2 h after carrageenin treatment. At this time the control Δ reaction time for carrageenin was 15.0 ± 1.3. Animals injected with prostaglandin E_2 i.c.v. showed a significant increase ($P < 0.05$) in hyperalgesia, 19.5 ± 1.3 and 24.0 ± 0.8 for 10 or 100 ng, respectively (n = 5). In a paw injected with saline, such intraventricular injections of prostaglandin E_2 cause a slight transient hyperalgesia which receeds after 2 h (see also table 2).

3.7. Effect of prostaglandin E_2 (PGE_2) administered i.c.v. on the hyperalgesia induced by i.pl. injection of prostagladin E_2

The intensity of the hyperalgesia induced by three consecutive i.pl. injections of PGE_2 (100 ng), given 1 h apart, was enhanced by i.c.v. administration of PGE_2 2.5 h after the first injection (table 2). The third i.pl. injection of PGE_2 did not further increase the intensity of hyperalgesia. Treatment of the animals with indomethacin did not block the direct hyperalgesic effect of PGE_2 in contrast to what occurred with carrageenin hyperalgesia (see table 1).

3.8. Effect of a late i.c.v. and i.pl. injection of a prostaglandin antagonist on carrageenin hyperalgesia

Fig. 5 shows the effect of a prostaglandin antagonist (SC-19220) on carrageenin hyperalgesia. I.pl. or i.c.v. administration of the prostaglandin antagonist (at the 2 h time point) blocked the increase in hyperalgesia

TABLE 2

Influence of indomethacin on the hyperalgesic effect of i.pl. and i.c.v. administration of prostaglandin E_2.

Prostaglandin (PG) was given by either i.pl., i.c.v. or both routes. PG i.pl. treatment: 3 successive injections of 100 ng at 0, 1, 2 h respectively. The PG i.c.v. injection (100 ng) was made after the last plantar injection. Saline (S) was given as control injection. Indomethacin (2 mg/kg) was given at the beginning of the experiment. n of each group = 6. Δ response time: $\bar{x}$ ± S.E.M. sec.

Treatment		Time (h)					
I.pl.	I.c.v.	1	2	3	4	5	6
Control							
S	S	0.9 ± 0.1	0.8 ± 0.2	0.8 ± 0.1	0.9 ± 0.1	0.8 ± 0.1	0.7 ± 0.1
PG	S	4.3 ± 0.2	16.7 ± 0.3	17.6 ± 0.4	17.5 ± 0.3	17.2 ± 0.3	17.0 ± 0.3
S	PG	0.9 ± 0.1	0.7 ± 0.1	4.1 ± 0.3	1.1 ± 0.1	0.8 ± 0.1	0.7 ± 0.1
PG	PG	4.3 ± 0.2	15.6 ± 0.3	19.1 ± 0.1	22.2 ± 0.6	21.7 ± 0.7	20.9 ± 0.7
Indomethacin							
S	S	0.8 ± 0.1	0.8 ± 0.1	0.6 ± 0.1	0.9 ± 0.1	0.7 ± 0.1	0.7 ± 0.1
PG	S	4.4 ± 0.2	15.3 ± 0.2	16.3 ± 0.2	16.3 ± 0.4	16.2 ± 0.3	15.7 ± 0.3
S	PG	0.8 ± 0.1	0.9 ± 0.2	4.3 ± 0.3	1.3 ± 0.1	1.0 ± 0.1	0.7 ± 0.1
PG	PG	3.9 ± 0.3	15.0 ± 0.3	19.4 ± 0.4	24.3 ± 0.5	23.5 ± 0.7	22.8 ± 0.3

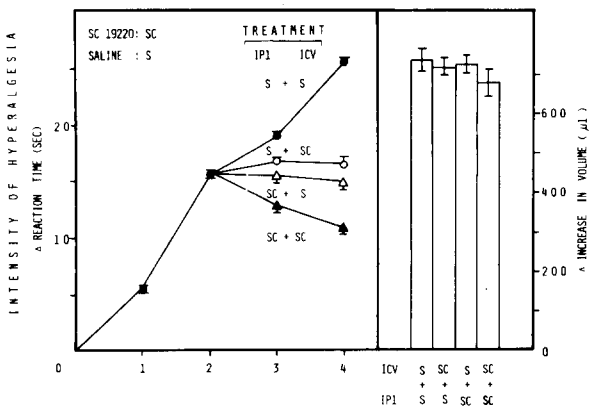

Fig. 5. Effect of i.c.v. or i. pl. SC 19220 on carrageenin effects. Both paws were injected with carrageenin and the antagonist (10 ng) was given at the 2 h point. The left panel shows the development of hyperalgesia and the right panel the measurement of oedema made at 4th h. Treatment i.pl. (intraplantar) and i.c.v. (intracerebroventricular).

which normally occurred between the 2nd and 4th of carrageenin inflammation. The combination of central and peripheral administration produced a more intense blocking effect which reached values equivalent to those obtained with the highest doses of antialgesic agents (see table 1). The antagonist caused an antialgesic effect without interfering with the oedema.

4. Discussion

The term antialgesia is used in this paper to denote the effect of non-steroid anti-inflammatory agents in contrast with the term analgesia, which should be properly used for the effect or narcotic analgesic drugs. The antialgesic (antialgic, antalgic) effects of non-steroid anti-inflammatory agents has only been shown in the presence of inflammation, while an analgesic agent increase the pain threshold for both inflamed and normal tissues (Winter and Flataker, 1965). The data presented here for the systemic, local and central administration of paracetamol, phenacetin, aspirin and indomethacin support this concept. Furthermore, small doses of a major tranquilizer (chlorpromazine) and a CNS depressant (nembutal), in spite of their visible effect on spontaneous movements, had no appreciable analgesic effect. They prolonged the reaction time of both control and inflamed paws. However, as these increases were identical, subtraction of the control values from those obtained with the inflamed paws did not show significant variation in the intensity of hyperalgesia (Δ reaction time). An intraventricular injection of a centrally acting analgesic such as morphine affected the reaction time of both paws. Those values were much greater than before the administration of the drugs (negative reaction times) but there was no difference when the reaction time of controls was subtracted from the reaction times of the inflamed paws.

As early as 1899, Dreser claimed that aspirin-like drugs acted on the CNS, but experimental evidence for this action is relatively scarce. As most of the evidence is bases on systemic administration, there is always the possibility that the action of these drugs could result from a peripheral effect because the type of stimulation used, radiant energy or electrical shock by means of implanted electrodes (Bonnycastle et al., 1953; Dubas and Parker, 1971), could cause local sensitization by prostaglandin release. Other reports however indicated that some drugs may have an analgesic action independently of their anti-inflammatory activity (Vinegar et al., 1975; Brune et al., 1974).

Our experiments clearly showed a central effect of aspirin, paracetamol, phenacetin and indomethacin on the hyperalgesia induced by carrageenin. When the drugs were administered simultaneously into both sites into the animal ventricles and into the paws) the results were suggestive of a synergism rather than of a simple addition of effects. The values observed for the combination (50 μg each i.c.v. + i.pl.) of aspirin, paracetamol and phenacetin (fig. 3) were of the same order of magnitude as

those for 400 μg administered either i.c.v. or i.pl. (table 1). The combined administration of indomethacin (10 μg each route) was as effective as that of 100 μg given either i.pl. of i.c.v. For most of the drugs used, this combined effect was of the same order of magnitude as that obtained with the highest doses given by any one of the three routes. Only an additive effect was observed with paracetamol probably because the simple addition of its central and peripheral effects was already of the same order of magnitude as the maximal antialgesic effect observed in this model. Our experiments do not permit to evaluate the relative contirbution of the central action to the overall antialgesia induced by a systemic administration of aspirin-like drugs. Central action might be more relevant in those inflammatory processes in which there is synergism, rather than a simple addition, between the central and peripheral effects. In such a case, a strong antialgesia would be produced by a small concentration of aspirin-like drugs at both sites.

Our results suggest that a previous inflammation is able to trigger a mechanism which accelerates the development of hyperalgesia induced by a second inflammatory stimulus. In contrast, the oedematous response is markedly reduced, a well-established counter irritant effect (see Atkinson and Hicks, 1975). Previous treatment of one paw reduced the oedema caused by a second injection of carrageenin in the contralateral paw, while it had no effect on the intensity of the hyperalgesia but shortened the time necessary for it to reach its plateau. We suggest that this mechanism involves the release of prostaglandins in the CNS; this suggestion is based on the antialgesic effect shown for an intraventricularly given specific prostaglandin antagonist (SC-19220; Sanner, 1974). The possibility of local modulation of hyperalgesia by the CNS has long been suggested (Chapman and Goodell, 1964) and it is known that electrical stimulation of frog hind paws (Ramwell et al., 1966) or cat radial nerves (Ramwell and Shaw, 1966) induces prostaglandin formation in the spinal cord and sensory cortex.

Due to the inherent difficulties in measuring increased levels of prostaglandins in CNS, we have tried to mimic carrageenin-induced hyperalgesia by intraventricular and intraplantar administration of prostaglandins. Prostaglandin E_2 was chosen for these exerpiments because it is the main product generated by the incubation of arachidonic acid with brain microsomal preparations (Flower and Vane, 1972). Our results showed that successive injections of PGE_2 into the paw or a single intraventricular injection did not match the hyperalgesic effect of carrageenin, which was obtained by i.c.v. + i.pl. administration. It was also observed that giving PGE_2 i.c.v. before the full development of carrageening hyperalgesia, markedly enhanced its effect.

Collier and Roy (1974) postulated the involvement of prostaglandin release in the CNS in the mechanism of morphine analgesia. They proposed that morphine analgesia resulted from a blockade of the increase of cyclic AMP which could be induced by an endogenous release of prostaglandins. In fact, centrally applied prostaglandin E_1 has been shown to antagonise morphine analgesia (Ferri et al., 1974). We believe that aspirin-like drugs and morphine have different modes of action. Morphine has a depressor effect on the central mechanisms involved in nociception while non-steroid anti-inflammatory agents, by inhibiting the synthesis of prostaglandins, prevent the central and peripheral sensitization of these mechanisms.

While our studies were in progress, Sandrini and Zanoli (1977) showed that low doses of intracerebrally given salicylates had an antialgesic effect in the writhing test with mice. Since sodium salicylate is known to be a poor inhibitor of cyclo-oxygenase in vitro (Flower and Vane, 1972), the results of Sandrini and Zanoli (1977) apparently contradict the suggestion made in this paper that the antialgic effect of central non-steroid anti-inflammatory drugs is exerted through an inhibition of prostaglandin generation.

However, when administered in vivo, salicylates effectively decrease the content of prostaglandins in inflammatory exudates (Willis et al., 1972; Higgs et al., 1976). A hypothesis to explain this fact would be the intracellular acetylation of salicylates near the site of prostaglandin synthesis.

Our results also seem to contradict those of Lim et al. (1964), who could not show a central effect of aspirin-like drugs. But in their model there was no inflammation and, as we pointed above, the central component of hyperalgesia is only detectable in the presence of an inflammatory process. Using the dog spleen model of Lim et al. (1964), we have shown that an accute and short-lasting sensitization of chemoreceptors occurs because the administration of bradykinin induces a local release of prostaglandins. Aspirin-like drugs have been shown to act by blocking this local release and, consequently, chemoreceptor sensitization (Ferreira et al., 1973).

In conclusion, our results indicate that the inflammatory hyperalgesia induced by carrageenin injected into the rat paw has two components suggested to be due to prostaglandin release: a peripheral one, due to the sensitizing action of pain receptors and a central one, involving the participation of central pain circuits. It is an established fact that the prostaglandin synthetase enzymes (cyclo-oxygenase) from different tissues show differential sensitivity towards aspirin-like drugs (Flower and Vane, 1972). Paracetamol is equivalent to and dipyrone is more potent than aspirin aginst CNS prostaglandin synthetase (Dembinska-Kiec et al., 1976). In man, these two drugs are known to be devoid of action upon arthritic swelling, although they are partially effective on joint pain. Aspirin has both actions (see Woodbury and Fingl, 1975). However in the rat, paracetamol and phenacetin are anti-oedematogenic (Vinegar et al., 1976) and capable of reducing the level of prostaglandin in inflammatory exudates (Higgs et al., 1976). Flower and Vane (1972) proposed that the antialgesic effect of these drugs was due to their selective action on nervous tissue prostaglandin synthetase enzymes. We suggest that this effect could be at the pain sensory nerve endings and/or in the central nervous system. The relative contribution of each hyperalgesic component probably varies according to the species, site, type and intensity of the injurious stimuli. The central component has been shown here to occur in the rat paw carragenin test and in the writhing test in mice (Sandrini and Zanoli, 1977), but is relevance remains to be demonstrated in other inflammatory reactions in which aspirin-like drugs are effective antialgesics.

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