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L. Buche and D. Gallaire

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16. Abstract

In order to provide more information on the genesis of ulcers in restrained rats, an investigation has been made of the relationship between the protective effects of all substances examined vis-à-vis ulcers in restrained rats and their elective or secondary pharmacologic effects.

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ULCERS IN RESTRAINED RATS
STUDY OF PROTECTIVE SUBSTANCES

L. Buche and D. Gallaire
Pharmacology Institute

The pathogenesis of gastric ulceration in restrained rats is /537* still not understood. We do know, however, that there is an influence in the production of these lesions from the vagal nervous system (9, 10, 11, 12, 13, 45, 46) and from factors originating in the central system (9, 10, 47, 48).

Having at our disposal a technique described in previous publications (15, 18) inducing gastric ulcerations after immobilization during a short period, has made it possible to determine the protective action of various substances which have pharmacologic effects during the entire restraining period. We have used substances capable of either peripheral parasympatholytic, sympatholytic, ganglioplegic, spasmolytic effects, or central, hypnotic, tranquilizing, neuroleptic, analgesic effects.

Hoping to provide additional information relating to the genesis of ulcers in restrained rats, we have attempted to determine a relationship between the protective effects of all substances examined vis-à-vis ulcers in restrained rats and their elective or secondary pharmacologic effects.

SUBSTANCES USED AND TECHNIQUES /538

I. Substances

The substances examined are capable of an elective effect on either the peripheral or central nervous system.

Substances with peripheral effects include:

1. Four parasympatholytics: three ester-amines, atropine sulfate, dihexyverine or cyclchexyl-1-cyclohexyl-carboxylate of piperidoethanol

*Numbers in the margin indicate pagination in the foreign text.

(Spasmodex*) and J.L. 1344 or phenyl-1-cyclohexyl-carboxylate of piperidinothanol in the form of chlorhydrates, a quartenary ammonium, benzylonium bromide, bromide, bromide benzylic ester of N-diethyl-1-hydroxypyrolidinium-3 (Portyn*).

2. Two sympatholytics: one acting mainly on the alpha receptors, dibenamine, N, N' dibenzyl-β-chlorethylamine, in the chlorhydrate form in a pH 2 solution, the other acting as an inhibitor of the β receptors, propranolol, isopropylamino-1 (x naphthyloxy)-3 propanol-2, in the chlorhydrate form (Inderal*).

3. One ganglioplegic: pentamathonium, dibromide of pentamethylene-di-(trimethylammonium).

4. One papaverinic spasmolytic: papaverine hydrochloride.

Substances with central effects include:

1. Six hypnotics: one aldehyde, chloral hydrate; one urethane, ethylurethane; four barbiturics: butobarbital (Soneryl*); tetrabarbital (Butysedal*), sodic pentaobarbital or mebubarbital (Nembutal*), phenobarbital (Gardenol*). Butobarbital, tetrabarbital and phenobarbital are solubilized in the presence of sodium carbonate.

2. Two tranquilizers; carbamate of methyl-3-pentynol-3, (N-Oblivon*) and meprobamate, procalmadiol, dicarbamate of methyl-2-propyl-2 propane-diol-1-3 (Equanil*).

3. Six neuroleptics: chlorpromazine, chloro 3-(dimethylamino-3'-(propyl)-10-phenothiazine (Largactil*), in the chlorhydrate form; reserpine in the pure crystallized alkaloide form, (Serpasil*), in a solution with a solvent having the following composition: citric acid, 2.5 mg, polyethylene glycol 300, 100 mg; distilled water q.s.p. 1 ml; four derivatives of butyrophenone, haloperidol, R.1625, 4'-fluoro-4(4'-chloro)-phenyl-piperidino))-butyrophenone (base); triperidol, R.2498, 4'-fluoro-4-4-hydroxy-4-(3'-trifluoromethyl-phenyl)-piperidine-butyrophenone (chlorhydrate); benperidol, R.4584, 1-(γ -(4fluoro-benzoyl)-propyl)-1-oxo-4-phenyl-2, 4, 8-trazaspiro-(4,5)-decane

(chlorhydrate).

4. One analgesic: dextromoramide (Palfium)* in the bitartrate form.

II. Technique /539

The technique used to produce gastric ulcerations in restrained rats has been previously described (15, 18). Animals which underwent a 24 hour hydrated fasting beforehand are immobilized for two and one half hours at an ambient temperature of 21 + 4°C.

We experiment on female rats of Wistar stock, with a weight varying from 100 to 130 g; always taken from the same breeding.

The substances under examination are administered intraperitoneally, usually fifteen minutes after the beginning of immobilization. The hypnotics are injected fifteen minutes before restraining the rat, which makes it possible to avoid using ether anaesthesia to immobilize the animals. More exceptionally, we have used intravenous or oral routes. The volume administered varies from 0.25 to 0.50 ml/100 g of weight. Experiments are performed most often on groups of at least twenty rats. The same day the rats are treated, a group of control rats are administered a physiological solution.

Changes in the percentage of animals developing ulcerations and the average index, which accounts for the severity of the lesions, are calculated relative to the control animals and their statistical meaning is determined according to the process described by FAVERGE (25).

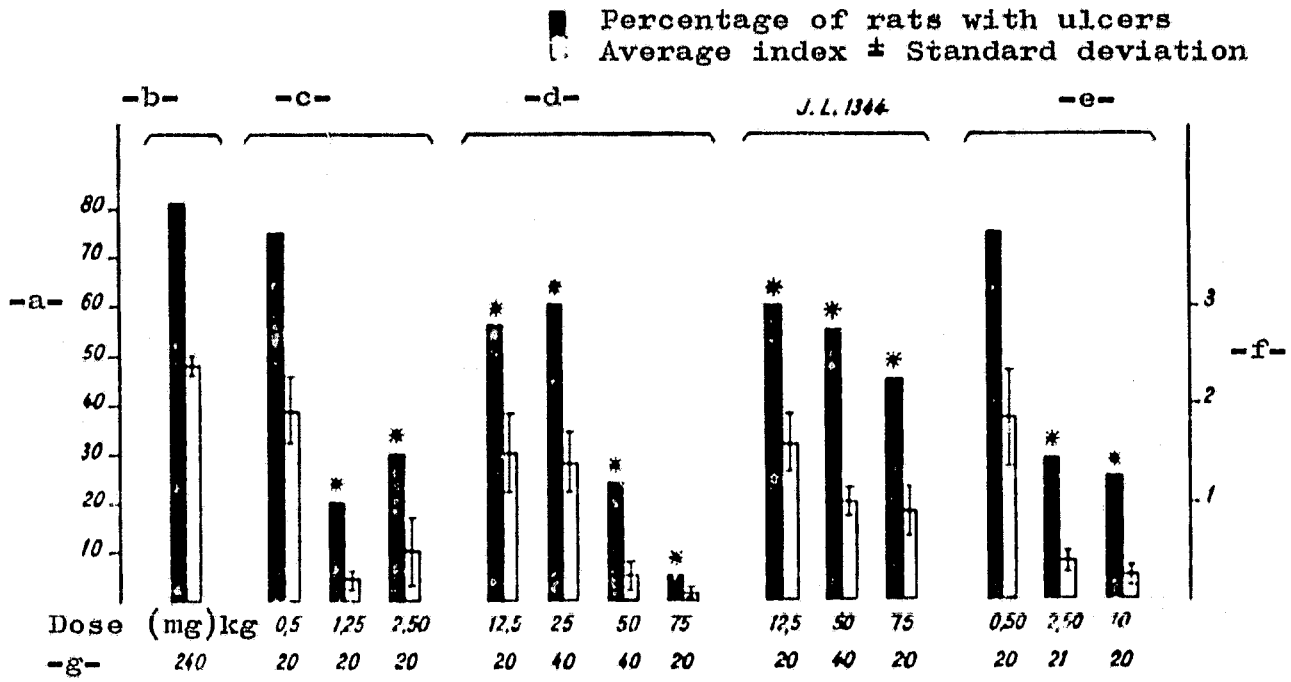
RESULTS AND REMARKS

A. Substances With Peripheral Effects

1. Parasympatholytics

The four parasympatholytics examined, administered intraperitoneally, exert various degrees of protective action vis-à-vis

the ulceration in restrained rats; the average ulceration index varies as a function of the decline in the percentage of rats stricken with ulcerations (fig. 1). They may be classed by order of decreasing pro-



Key: a-Percentage of rats showing ulcerations; b-Control rats; c-atropine sulfate; d-Dihexyverine; e-Benzylonium bromide; f-Average index; g-Number of rats ♀

Figure 1 - Action of parasympatholytic substances in the production of ulcerations in restrained rats, which are administered intraperitoneally, Significant results are marked by an asterisk (P less than 0.01).

tective action as follows: atropine sulfate (*) greater than benzylonium bromide greater than dihexyverine greater than J.L. 1344, since their equiactive doses are 1.25 mg/kg, 2.50 mg/kg, 50 mg/kg and more than 75 mg/kg.

We thought it would be of interest to compare these results with the anticholinergic effects of these substances, determined on the isolated duodenum of the rat by the Jeannne LEVY and SIOU (42) technique and their mydriatic effects in the rat following intraperitoneal administration.

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*Atropine sulfate is about 40 times more active than dihexyverine through the oral route and through the intraperitoneal route.

On the isolated organ, the hierarchy of anticholinergic effects (27) is comparable to that established from the protection vis-à-vis the ulceration in restrained rats. This is also the case for the mydriatic effects determined in vivo; let us note in addition that atropine sulfate (0.5 mg/kg), benzylonium bromide (1.25/kg) and dihexyverine (10 mg/kg) are mydriatic at doses below those required to block the production of ulcerations in restrained rats.

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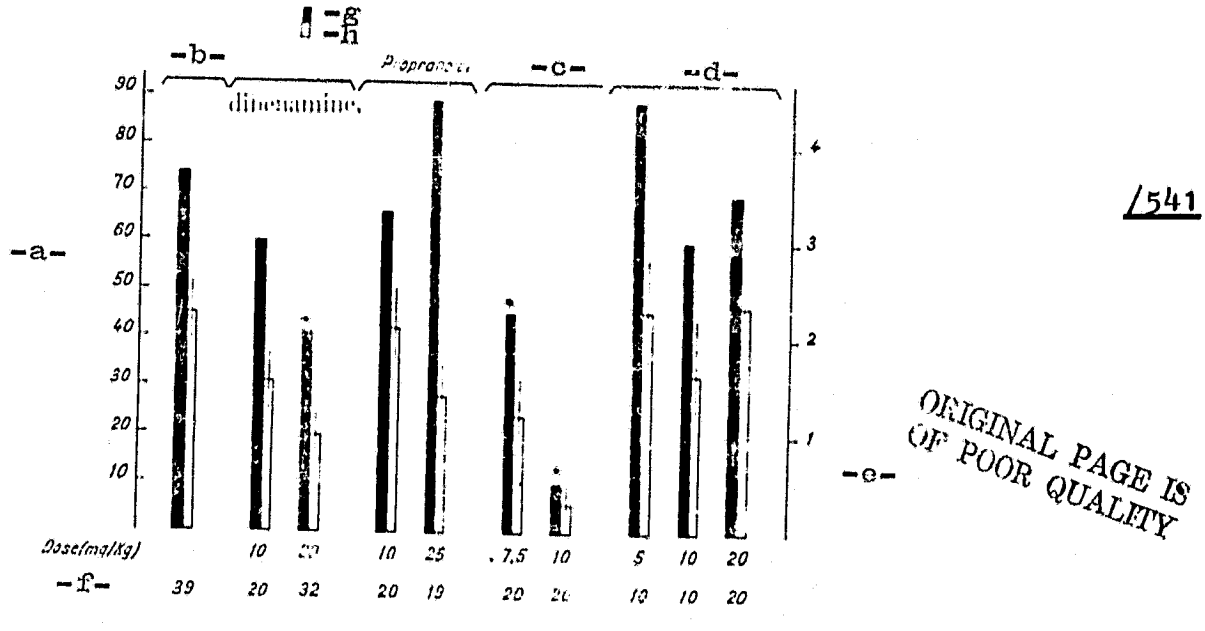
2. Sympatholytics

Dibenamine, which inhibits the alpha-receptors when injected intraperitoneally, in one minute with a dose of 20 mg/kg (27% of DL_{50}), exerts a certain degree of protection vis-à-vis ulceration in restrained rats (fig. 2). We have verified that this dose administered to an



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Key: a-Percentage of rats showing ulcerations; b-Control rats; c-Pentamethonium dibromide; d-Papaverine hydrochloride; e-Average index; f-Number of rats ♀; g-Percentage of rats showing ulcerations; h-average index ± standard deviation.

Figure 2 - Action on the production of ulcerations in restrained rats of dibenamine, propranolol, pentamethonium dibromide and papaverine hydrochloride administered intraperitoneally. Significant results are marked with an asterisk (P less than 0.01).

anaesthetized and atropined rat in the same conditions reduces the hypertensive effects of adrenaline by 50% for a period of more

50% for a period of more than 60 minutes, after a latent time of 20 to 30 minutes. A dose of 10 mg/kg does not modify the adrenaline effects.

Let us recall that dibenamine has central stimulating properties: /542 doses of about 35 mg/kg administered intravenously into the mouse induces convulsions (44); it creates agitation, trembling and interaggressivity in the rat and a state of hyperexcitability in the mouse (28).

Propranolol, which inhibits the receptors, does not reduce the frequency of ulcerations (fig. 2), even with a dose of 25 mg/kg, representing 33% of the DL_{50} (determined by intraperitoneal injection practiced in one minute). In the anaesthetized rat, 10 and 25 mg/kg of propranolol eliminates the hypotensive effects of isoprenaline in 10 minutes, whereas the hypertensive effects of adrenaline are potentialized.

This substance is capable of central depressive and anticonvulsive properties in the rat and the mouse at doses ranging between 5 and 40 mg/kg administered subcutaneously (40).

3. Ganglioplegic

Pentamethonium dibromide substantially reduces the percentage of animals with ulcerations and the average index with a dose of 7.5 mg/kg; the intensity of this protective action increases with a dose of 10 mg/kg (fig. 2). With the same dose and same means of administration, we have found an extended ganglioplegic in the anaesthetized and atropined rat: hypertension induced by intravenous injection of phenoxycholine iodide (115 µg/kg), excito-ganglionic (44) is fought for more than 80 minutes.

Let us recall that BRODIE and VALITSKI (14) use a test which associates coldness with restraining in the rat to prevent by administering mecamylamine (Inversine*), the appearance of digestive hemorrhaging which occurs in the absence of this ganglioplegic. ANICHKOV and ZAVODSKAYA (2) bring to light the protective action

of hexamethonium vis-à-vis gastric ulcerations of reflex origin induced by applying clamps on the rat's duodenum.

4. Papaverinic Spasmolytic

At doses varying from 5 to 20 mg/kg, papaverine hydrochloride does not influence the production of ulcerations (fig. 2). According to the MACHT and BARBA-GOSE technique (43), it does not slow down the intestinal tract in the rat, even with a dose of 30 mg/kg (50% of DL_{50}).

B. Substances With Central Effects

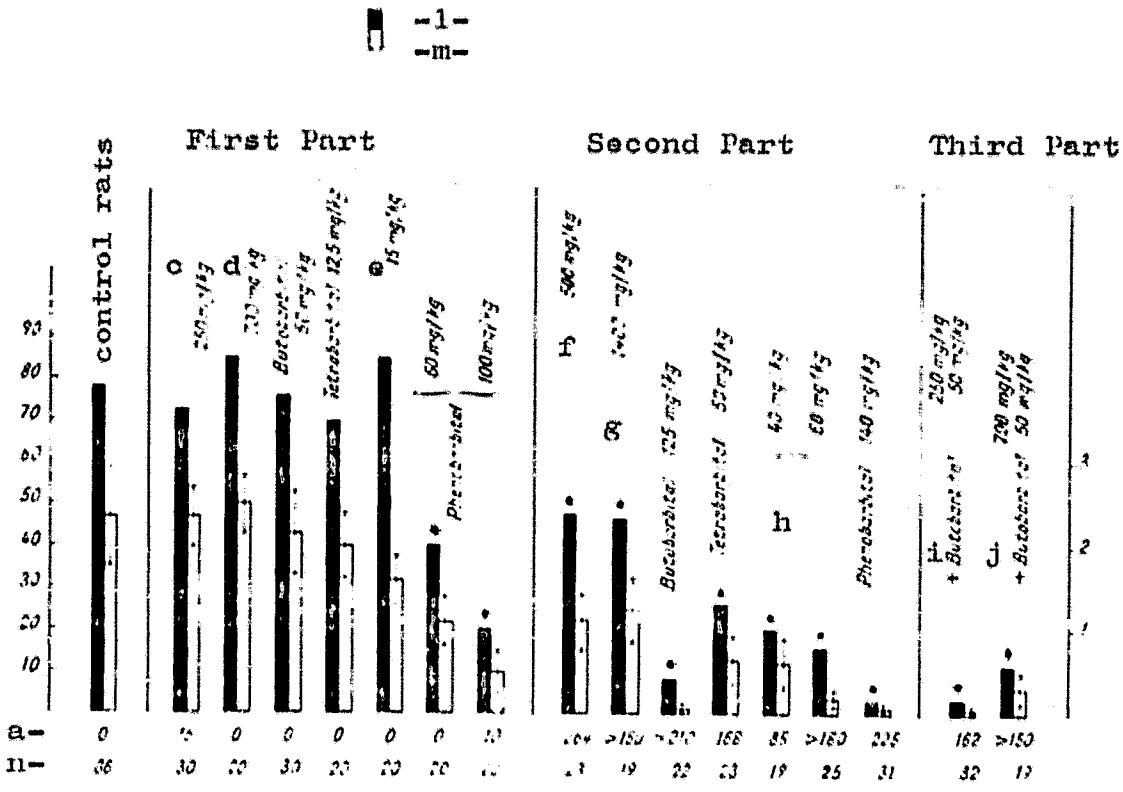
1. Hypnotics

Mebubarbital has been experimented by BONSFILS and associates (10), HANSON and BRODIE (29), SIMLER and SCHWARTZ (49), who use a restraining of 24 hours. The first authors find a moderate reduction in the percentage of ulcerations after administering a barbiturate at the beginning of the restraining period. SIMLER and SCHWARTZ (49) show that rats are protected for more than 24 hours when treated one day prior to the restraining with a mebubarbital dose inducing a sleep of 5 to 6 hours.

On figure 3, we have summarized the results relating to the frequency of ulcerations and the average index after administering six hypnotics (*) and combinations of chloral hydrate-butobarbital, urethane-butobarbital (16). We have shown on the same figure the sleeping period induced by the doses used. We have used inactive or efficient liminar doses inducing an experimental sleep of 10 to 15 minutes together with strong doses, whether fractioned or not, inducing a sleeping period just as long or longer than the restraining period, i.e. 150 minutes, With these latter doses, it has been observed that a mortality of 5 to 20% is characteristic with most hypnotics (16). /543

At efficient liminar or inactive doses, phenobarbital (60 mg/kg, or 60% hypnotic liminar dose) is the only active hypnotic; it reduces

*It has been administered intraperitoneally, except for one phenobarbital dose of 140 mg/kg injected intravenously.



Significant results are marked with an asterisk (P less than 0.01).

First part: with nonhypnotic or efficient liminary doses.
Second part: with doses inducing a sleeping period equal to or longer than the restraining period.
Third part: by combining.

Figure 3 - Action of hypnotic substances on the production of ulcerations in restrained rats.

the percentage of animals with ulcerations and the average index (fig. 3, first part). Let us recall that phenobarbital has important anticonvulsive properties, especially in the rat sensibilized by nicotinylhydrazide, where it fights acoustic epilepsy with a dose of 10 mg/kg administered intraperitoneally (19). Moreover, tetrabarbital, which is ineffective vis-à-vis ulcerations in restrained rats with a nonhypnotic dose of 12.5 mg/kg, fights acoustic epilepsy with a dose of 2.5 mg.kg (19).

When the experimental sleep lasts throughout the restraining period, all of the substances used exert a protective action, except for the special case of urethane. The intensity of the protective action depends on the type of hypnotic used. Barbiturates are much more active than chloral hydrate; they are placed by order of decreasing activity as follows: phenobarbital greater than mebubarbital greater than tetrabarbital greater than butobarbital greater than chloral hydrate (fig. 3; part 2). Whereas barbiturates decrease the percentage of animals striken with ulcerations along with the average index, this is not the case with chloral hydrate. The only significant result of this latter substance relates to the number of animals protected. Moreover, these results may be compared with those obtained by ANICHKOV and ZAVODSKAYA (2): vis-à-vis the gastric ulceration of reflex origin induced in the rat by applying a clamp on the duodenum: the phenobarbital exerts a preventive action, whereas chloral hydrate has no effect.

A combination of the inactive doses of chloral hydrate and butobarbital (fig. 3; part 3) causes the sleeping period to last throughout the restraining period, due to the effect of potentialization, and exerts a considerable protective action (percentage of animals protected and average index).

The case of urethane must be distinguished from that of other hypnotics. In fact, urethane, which is nonulcerogenic with a dose of 700 mg/kg, becomes ulcerogenic with a dose of 1,400 mg/kg. In this case, it causes gastric ulcerations in 42% of the animals which are not restrained. For restrained rats, on the other hand, the ulcerogenic effects of urethane are not combined with the restraining effects. The number of animals with ulcerations is reduced to 48%, which is very close to the results with the same dose of urethane for non-immobilized animals. Accordingly, it is possible to distinguish the ulcerogenic effects of urethane from its protective action vis-à-vis the ulceration of restrained rats. On the other hand, by combining a nonulcerogenic dose of urethane (700 mg/kg) with butorbarbital, the number of animals with ulcerations decreases by 11% with an average index of 0.3 (fig. 3, part 3). /545

2. Tranquilizers

With a benactyzine dose of 24 mg/kg, HANSON and BRODIE obtain a considerable protection in rats restrained for four hours after a 48 hour fasting. ANICHKOV and GRECHISKIN (1) show there is an inhibiting action exerted by benactyzine on the gastric secretion induced by acetylcholine, since the two substances are injected by intracarotid route.

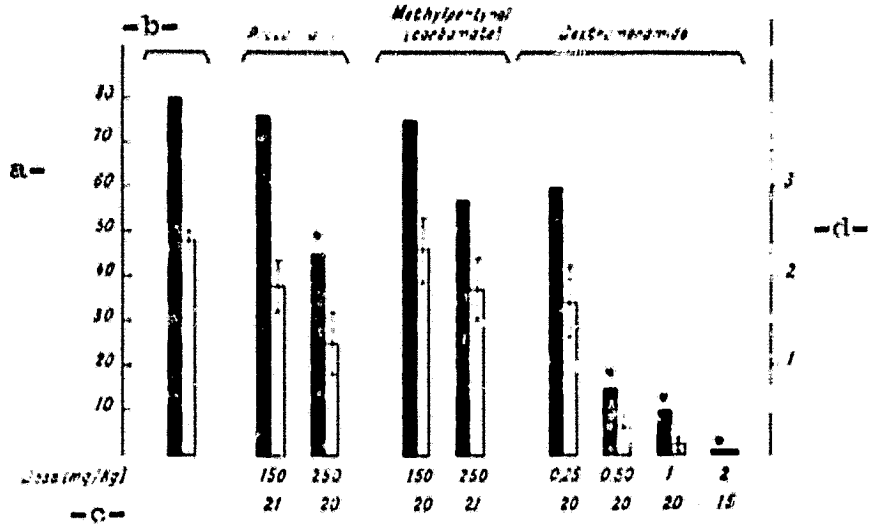
According to HAOT and associates (30), a dose of 50 mg/kg of chlordiazepoxide permits a 50% reduction in the percentage of ulcerations caused by a 5 to 6 hour restraining. /546

In experiments made with meprobamate (procalmadiol) and methylpentynol carbamate, a 250 mg/kg dose of meprobamate ensures a certain degree of protection (fig. 4). Even a 250 mg/kg dose of methylpentynol, which induces a state close to sleep during the restraining period, does not exert a significant protective action (fig. 4).

Let us point out that a 35 mg/kg dose of meprobamate and methylpentynol administered intraperitoneally, exerts a protective action vis-à-vis the acoustic epilepsy in rats sensitized with nicotinylhydrazide (19).

3. Neuroleptics

Reserpine, capable of ulcerogenic properties by itself (17, 38, 39, 53), does not exert a protective action vis-à-vis ulcers in restrained rats; it can, however, increase the frequency of ulcers (7, 17, 21). Chlorpromazine has been experimented with doses varying between 5 and 20 mg/kg by FONTAN and associates (26), HANSON and BRODIE (29), BONSFILS and associates (8), BUCHEL and GALLAIRE (15, 17). Authors are unanimous to state that it has a protective action in rats restrained for 2 1/2 to 24 hours. The other derivatives of phenothiazine (thioridazine (8), methopromazine (26), thioproperazine (8.3)) decrease the frequency of ulcers in rats restrained for seven hours. When the animals are restrained for 24 hours, thioproperazine has no effect, even if it is repeatedly administered during the restraint.



Key: a-Percentage of rats with ulcers; b-Control rats; c-Number of rats & d-Average index.

Figure 4 - Effects of two tranquilizers and one analgesic on the production of ulcers in restrained rats. Significant results are marked with an asterisk (P less than 0.01).

Levomepromazine and acepromazine (26) do not exert a preventive action and even seem to increase the frequency of ulcers.

The cataleptogenic dose of chlorpromazine administered intraperitoneally varies from 3.3 mg/kg to 16 mg/kg (5), depending on the test used. From these results, doses of chlorpromazine (5 to 20 mg/kg), which were shown to be protective vis-à-vis ulcers in restrained rats in our experiments (17), may be considered as cataleptogenic. Furthermore, doses of 2 and 5 mg/kg of chlorpromazine, administered intraperitoneally in the rat, exert sedative effects, since they potentialize the experimental sleeping periods induced by chloral hydrate and hexobarbital (20), respectively.

We have examined four derivatives of butyrophenone, which were synthesized and studied by JANSEEN and his associates (32, 33, 36, 39), for their action on the production of ulcers in restrained rats in

comparison with reserpine and chlorpromazine. They are haloperidol, triperidol, benzperidol and spiroperidol with doses from 0.1 to 10 mg/kg (17). These substances have cataleptogenic properties (36, 51). We have thus verified that a 0.1 mg/kg dose of benzperidol administered intraperitoneally, induces a moderate catalepsy one hour after the injection and that a 0.1 mg/kg dose of all of these substances creates cataleptic states after 30 and 60 minutes, which become excessive between the first and second hour. /547

None of these derivatives exerts an ulcerogenic action with the strongest doses used, whereas it is produced in 100% of the animals with the cataleptogenic dose of 5 mg/kg of reserpine (17).

We may summarize as follows the results obtained for the preventive action vis-à-vis ulcers in restrained rats. Doses of 0.2 to 5 mg/kg of haloperidol reduces neither the frequency nor the severity of the ulcers; with a dose of 10 mg/kg, which is highly cataleptogenic, we observe a moderate decrease (60% instead of 81%), which is insignificant (0.01 less than P less than 0.05) in the percentage of ulcerated stomachs, without a modification in the average index. A similar action is observed for a 0.2 mg/kg dose of triperidol, whereas the administration of 1 to 5 mg does not produce a preventive action. A 0.1 mg/kg dose of benzperidol, which is already cataleptogenic, does not significantly modify the frequency of ulcers; it does, however, decrease the average index. A 1 mg/kg dose is without effect. A 0.2 mg/kg dose of spiroperidol reduces moderately, but significantly, the percentage of animals with ulcers; there is no protective action when the dose rises to 1 mg/kg.

None of the four butyrophenone derivatives exerts a regular and important protective action, regardless of the doses used: small doses slightly depress the motility of the animals, especially at the beginning of the restraining; strong doses create a cataleptic state. Under the same experimental conditions, we confirm both the protective action of chlorpromazine, the intensity of which is a function of the dose used (5 to 20 mg/kg) and the aggravating action of reserpine (1.5 to 2.5 mg/kg).

4. Analgesic

SIMLER and associates (50) have brought to light the inhibiting action of morphine vis-à-vis the frequency of ulcers in rats restrained for 24 hours.

We have used dextromoramide (16), an analgesic which has been synthesized and studied by JANSSEN and JAGNAU (34, 35). The calculated doses have varied from 0.25 to 2 mg/kg.

Dextromoramide exerts an important protective action (percentage of animals protected and average index) vis-à-vis ulcers of restrained rats, with a dose of 0.5 mg/kg. In the tests we have used, it is neither analgestic, nor catelptogenic, nor mydriatic, but blocks the intestinal tract in the rat.

With the heating plate of WOOLFE and MACDONALD (52), which was /548
modified by JACOB and BLOZOVSKI (31), we have obtained analgesia only with a 1 mg/kg dose (*) administered intraperitoneally; this action is characteristic in 70% of the rats and is effective on the average 60 minutes. With the same dose, 30% of the rats show a slight rigidity, whereas the dose of 2 mg/kg described by CHARPENTIER (22) and studied by BOISSIER and associates (6), produces a cataleptic state which lasts more than 150 minutes. A 1 mg/kg dose of dextromoramide creates a mydriasis, which is effective for 45 minutes.

A 0.5 mg/kg dose of dextromoramide, which is neither analgesic nor mydriatic, slows down the intestinal tract, since the importance of its action is equal to that induced by 1.03 mg/kg of base atropine. This is comparable to the results which JANSSEN and JAGENAU (34) observed in the mouse during the investigation of the intestinal tract: the action of dextromoramide is stronger than that of atropine sulfate, the doses of which are respectively 3.72 and 16.5 mg/kg. We may ask

*According to JANSSEN and JAGENAU (35), the dextromoramide dose administered subcutaneously, which causes analgesia in 50% of the rats, is 0.38 mg/kg with the heating plate test.

ourselves if the delay in the intestinal tract may be attributed to the anticholinergic properties of dextromoramide.

Given these experimental data, it seemed interesting to compare the papaverinic and atropinic actions of dextromoramide in vitro. A concentration in the isolated rat duodenum of 1.87×10^{-6} dextromoramide reduces barium-chloride-induced contractions by 50%. This action is much stronger than the papaverinic effect of atropine sulfate, which shows an effect only for concentrations of 400 to 500 X 10^{6}. Since a spasmogenic action of acetyl-β-methylcholine bromide with the same intensity as that induced by barium chloride is blocked by the same concentration of dextromoramide (1.87 X 10^{6}), it is not possible to attribute an atropinic spasmolytic action in vitro (27) to dextromoramide.

DISCUSSION

I. Substances With Peripheral Effects

A constant and important protection vis-à-vis the ulcer in restrained rats is obtained with all substances capable of anticholinergic properties exerted at the peripheral level (atropine sulfate, benzilonium bromide, dihexyverine, J.L. 1344) or at the ganglionic synapse level (pentamethonium). Even though this action occurs, for parasympatholytics at doses 2 to 5 times higher than those which induce mydriasis in the rat, its intensity is on a par with the degree of anticholinergic action. Moreover, we have checked that spasmolytic papaverinic without atropine properties does not affect the ulceration. /549

A small protection was obtained only with a sympatholytic acting at the level of the α adrenergic receptors, dibenamine. The mechanism of this protection remains undetermined even if we assume that dibenamine has the central stimulating properties described by certain authors (28, 44).

In summary, all of these results confirm the importance of the vagal nervous factor in the genesis of ulcers in restrained rats.

II. Substances With Central Effects

Among the central depressive substances which we have examined, phenobarbital and dextromoramide have proven to be quite effective vis-à-vis ulcers in restrained rats.

Phenobarbital reduces the frequency of ulcers at a dose which is not yet hypnotic, contrary to other barbituric derivatives, mebubarbital, tetrabarbital, butobarbital and chloral hydrate, which are effective only when they induce narcosis during the restraining period. As for urethane, which is ulcerogenic in the unrestrained animal, its protective action prevails when it is used at a dose which extends the sleep in the immobilized animal.

It is not very likely that the protective action of phenobarbital may be attributed to a peripheral anticholinergic effect, which we have not been able to illustrate on the isolated duodenum of the rat.

It also does not seem that the anticonvulsive properties of barbiturates may play a major role in the protective action of phenobarbital. The anticonvulsive actions of phenobarbital and tetrabarbital are similar in their different antiulceration effects. Accordingly, phenobarbital reduces the frequency of ulcers at a dose which is six times stronger than the anticonvulsive dose and 2 times weaker than the hypnotic dose. Tetrabarbital is ineffective at a dose which is five times stronger than the anticonvulsive dose.

Analgesic dextromoramide is considered an anticholinergic by some authors (22, 34). It combats the production of ulcers in restrained rats with a dosewhich is neither analgesic nor mydriatic in the rat, but which slows down the intestinal tract. Even though anticholinergic properties of dextromoramide have not been demonstrated on the isolated duodenum of the rat, it is not excluded that central anticholinergic effects slow down the intestinal tract and have a protective action vis-à-vis ulcers in restrained rats.

Among the neuroleptics tested, only chlorpormazine reduces without eliminating the production of ulcers in restrained rats; derivatives of butyrophenone do not significantly influence the frequency of ulcers, whereas reserpine is ulcerogenic. Moreover, at the doses used, all of these substances exert a cataleptogenic action; accordingly, the latter does not seem to play a determining role in antiulcerous effects.

For the two tranquilizers examined, even at doses much higher than the sedative doses, no observation was made of a preventive action with methyl-pentynol carbamate and a small degree of protection is obtained with procalmadiol.

In summary, the pharmacological reactives which we have used have not made it possible to define the levels at which a central factor is exerted in the antiulcerous effects of phenobarbital, dextromormide and chlorpormazine.

CONCLUSIONS

The antiulcerous action of substances electively exerting peripheral or central effects is determined in restrained rats.

1. The regular and considerable protection observed with parasympatholytics (atropine sulfate, benzylonium bromide, dihexyverine, J.L. 1344) and a ganglioplegic (pentamethonium) is a function of their anticholinergic properties. It is of less importance with dibenamine, a sympatholytic action on the adrenergic receptors.

2. Among the central depressive substances tested (hypnotics, tranquilisers, neuroleptics, analgesic), phenobarbital at a nonhypnotic dose, and dextromoramide at a nonanalgesic dose, show antiulcerous effects, which are found with chlorpromazine only at cataleptogenic doses.

3. The mechnanism of antiulcerous effects is discussed.

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