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Cimetidine Penetrates Brain and Inhibits Non-Opiate Footshock-Induced Analgesia

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HOUGH, L. B., S. D. GLICK AND K. SU. *Cimetidine penetrates brain and inhibits non-opiate footshock-induced analgesia.* PHARMACOL BIOCHEM BEHAV **24**(5) 1257–1261, 1986.—The inhibition of hindpaw (non-opiate) footshock-induced analgesia (HP-FSIA) by cimetidine, the histamine H_2-receptor antagonist, was characterized in rats, and the drug's presence in brain was demonstrated. Cimetidine (100 mg/kg, IP) inhibited HP-FSIA when administered 30 min before testing, but was inactive when testing began sooner (15 min) or later (1–4 hr) than this time. Lower doses (20 mg/kg) were also ineffective when given 30 min before testing, whereas higher doses (200 mg/kg) effectively inhibited the response. Increasing the footshock current from 4 mA (which elicited cimetidine-sensitive analgesia) to higher currents (5 and 6 mA) yielded cimetidine-insensitive analgesia. Administration of isotopically labeled cimetidine (100 mg/kg, IP, 30 min) yielded whole brain cimetidine levels of 1.95 nmols/g, respectively, with a brain/blood ratio of 0.017. These findings confirm a limited penetration of brain by cimetidine, and show that large peripheral doses of cimetidine are required to block brain H_2-receptors. The specific dose and time requirements for cimetidine to inhibit the HP-FSIA are probably attributable to the brain drug levels that can be achieved after peripheral administration.

Brain Analgesia Footshock Histamine H_2-receptor Cimetidine Stress

THE evidence is growing rapidly that endogenous histamine (HA) contributes to brain function, probably as a transmitter [10, 11, 18, 19, 25]. Because HA administered into brain causes analgesia [9], we recently investigated a role for brain HA as a mediator of analgesia. Although we found no evidence for HA as a mediator of *opiate* analgesia [12], we [13] and others [16] reported evidence that brain HA may mediate *non-opiate* analgesia elicted by certain types of inescapable footshock. Thus, the analgesia resulting from hindpaw shock was unaffected by large doses of the opiate antagonist naloxone, or by other transmitter receptor antagonists, but was inhibited by large peripherally-administered doses of the HA H_2 antagonists cimetidine, ranitidine and oxmetidine [13]. Because the latter are excluded from brain after lower doses given peripherally, we speculated that large doses of these drugs were necessary to penetrate the blood brain barrier [13]. As a part of these studies, we have characterized the pharmacological details of the inhibition of non-opiate footshock-induced analgesia (FSIA) by cimetidine, and demonstrated directly the presence of cimetidine in brain after its peripheral administration.

METHOD

Male Sprague-Dawley rats (250–300 g) were housed in groups of two and maintained on 12 hr light-dark cycles. Four to six hr into the light cycle, animals received intraperitoneal (IP) injections of either cimetidine (the injectable formulation of Tagamet® containing phenol, diluted appropriately with saline) or vehicle (phenol, 5 mg/kg in saline, shown to have no effect on FSIA, see [13]). In all cases, the identity of the injection solutions was blinded to the investigator. Each animal was placed in a cylindrical Plexiglas chamber on a shock grid, and the hindpaws exposed to scrambled DC current (4 mA unless specified otherwise) for 90 sec. Details of the method for hindpaw shock have been described [26]. Controls were placed in the same chamber and allowed to move freely on all paws with no shock. We found in unpublished studies that placing the animal on hindpaws in the test chamber without footshock did not cause analgesia. One min after shock termination, animals were restrained and tested by the tail immersion nociceptive test [21], with a water temperature of 54°C and a cutoff of 8 sec; each animal was used for only one measurement. The pretreatment time (varied in some experiments) was the interval between injection and analgesic testing. In order to verify the non-opiate nature of this analgesia (i.e., 90 sec of hindpaw footshock, 4 mA), the effect of naloxone (10 mg/kg, 10 min, IP) was studied in several experiments spanning the course of the present studies; in all cases, this treatment had no effect, confirming previous reports [13,26]. Because the experiments utilized a cutoff latency and the data are not normally distributed, the results are expressed as the median latency and interquartile interval for each group. Differences between groups were determined by the Wilcoxon rank sum test [27].

To measure brain and blood cimetidine levels, animals were injected (IP) with ^{3}H-cimetidine (1 mCi/kg, Amersham, Arlington Heights, IL) containing a total dose of 100 mg/kg. In each experiment, two control animals received the same total dose of cimetidine with no isotope. Twenty five min later (5 min before decapitation), each animal was anesthetized with methohexital (50 mg/kg, IP), and the chest

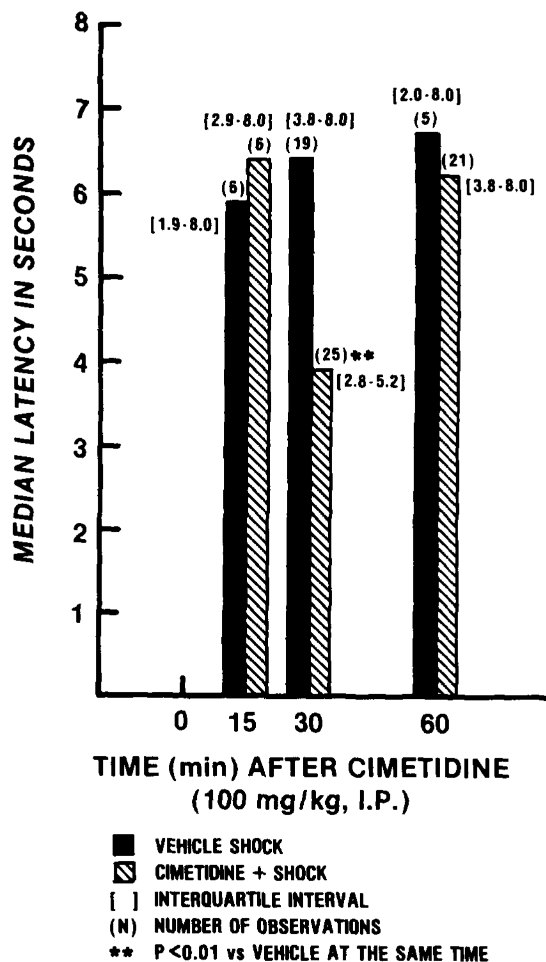

FIG. 1. Timecourse of antagonism of hindpaw footshock-induced analgesia by cimetidine. Rats received cimetidine (100 mg/kg, IP) or vehicle. After the elapsed times shown, they were exposed to hindpaw DC footshock (90 sec, 4mA), restrained and tested for their tail flick response. For each group, the median latency (in sec) for the number of animals in parentheses is shown, with the intraquartile interval for each group shown in brackets. The median latency for animals not shocked was 2.2 sec. The 30 min data were previously reported [13] and are included here for comparison.

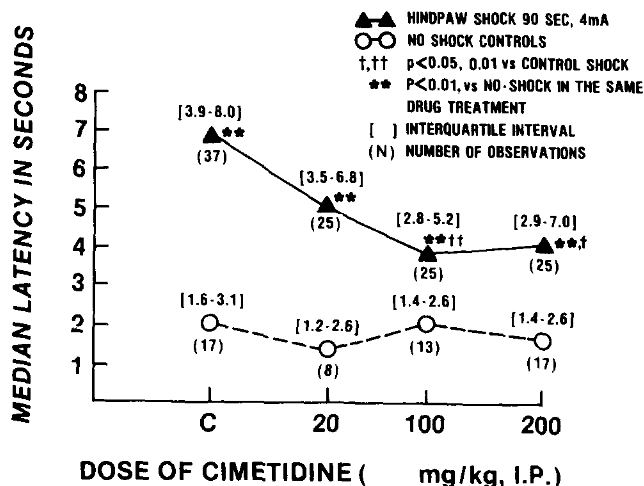

FIG. 2. Dose-response curve for the effect of cimetidine on hindpaw footshock-induced analgesia. Rats received the indicated dose of cimetidine (or vehicle control, C). Thirty min later, the animals were subjected to hindpaw shock (solid triangles) or no shock (open circles), and the tail flick latency measured. The shock and test treatments were identical with those of Fig. 1. The results after 100 mg/kg are also in Fig. 1.

cavity opened. Venous blood (3 ml) was collected by right atrial puncture and added to 0.1 ml of disodium EDTA (75 mg/ml). The left ventricle was then perfused with 150 ml of saline to remove blood from the brain, and the animal was decapitated. The brain was removed, homogenized in 4 volumes of an ice cold solution of acetonitrile-0.1 N HCl (4:1) containing 50 μg of unlabeled cimetidine, and centrifuged (30,000 g × 20 min). Duplicate aliquots (1.25 ml) of each supernatant fraction were added to conical polypropylene microcentrifuge tubes (volume=1.5 ml) which were evaporated to dryness at room temperature in a Savant vacuum centrifuge and resuspended in 0.05 ml of water.

To determine total brain radioactivity, 2 μl of this solution was mixed with 5 ml of scintillation cocktail (Formula 963, New England Nuclear, Boston, MA) and counted by liquid scintillation spectrometry. To determine the percent of radioactivity representing unmetabolized cimetidine in each sample, the remainder of each tube was applied to a separate lane of a Whatman LK6D silica gel plate, and analyzed by thin layer chromatography (TLC) using ethyl acetate-glacial acetic acid-n-butanol-water (1:1:1:1). The location of cimetidine on each lane (visualized by iodine vapor, R_f=0.54) was noted, and after the disappearance of the spots, each lane was divided (from origin to solvent front) into 0.5 cm portions. The silica gel from each portion was scraped from the plate, added to a scintillation vial, mixed with 0.5 ml of 0.5 N HCl, and counted as described above. In each experiment, two control animals received non-isotopic cimetidine, and were treated identically to the tracer group. Brain and blood samples from one of these animals were treated as blanks; samples from the other received aliquots of labeled cimetidine before processing. Total counts from the resuspended residues of the latter were compared with aliquots of the same isotope counted directly to measure and correct for any biological quenching and/or loss of isotope; recoveries calculated in this manner were 90% or greater. TLCs from the same group established the purity of the isotope used, and controlled for any influence of tissue on the separation; in all studies reported, the purity of the isotope determined in this manner was 93% or better. The percent of isotope representing unmetabolized cimetidine in each brain sample was determined by subtracting the silica gel blank from all samples, and dividing the net counts associated with the cimetidine spot by the total of net counts from each lane, corrected for the purity of the isotope determined in the same experiment. In a few experiments, the percent of radioactivity that remained as cimetidine was determined by TLC analysis with an additional solvent system (chloroform-methanol-ammonia, 60:35:4, cimetidine R_f= 0.67), and was found to be within 5% of the original results. Brain levels of cimetidine were calculated as the cimetidine levels equivalent to the total brain radioactivity multiplied by the percent of unmetabolized cimetidine found in each sample. This method for quantifying labeled cimetidine is similar to that described by Taylor *et al.* [23].

TABLE 1

EFFECT OF CIMETIDINE ON HINDPAW FOOTSHOCK-INDUCED ANALGESIA DELIVERED AT DIFFERENT CURRENTS

Current (mA)	Median latency in sec (N) Vehicle	[interquartile interval] Cimetidine
No Shock	2.3 (19) [1.7–2.5]	2.1 (19) [1.5–2.3]
3	5.3 (10) [3.1–8.0]*	—
4	6.9 (19) [3.8–8.0]*	3.9 (25) [2.8–5.2]*†
5	7.1 (20) [3.4–8.0]*	7.7 (21) [5.2–8.0]*
6	8.0 (6) [5.1–8.0]*	8.0 (6) [7.3–8.0]*

Rats were injected with cimetidine (100 mg/kg, IP) or vehicle. Thirty min later they were subjected to hindpaw footshock for 90 sec at various currents as described (see the Method section). Shown are the median latencies measured as described for the number of animals in parentheses. The interquartile interval of each group of data are shown in brackets. The 4 mA data also appear in Figs. 1 and 2.
*$p<0.01$ vs. No Shock with same drug treatment.
†$p<0.01$ vs. Vehicle at the same current.

Total radioactivity in blood (0.5 ml) was determined according to the method described by Kobayashi [15]. To determine the percent of unmetabolized cimetidine in blood, aliquots were mixed (1:1) with the acetonitrile-0.1 N HCl solution, centrifuged, and the resulting supernatant fractions were analyzed (0.05 ml per lane) by TLC with no concentration step. Cimetidine blood levels were calculated as described for brain.

RESULTS

Cimetidine (100 mg/kg, IP) significantly antagonized hindpaw FSIA when administered 30 min before analgesic testing, but was not effective when testing began sooner (15 min) or later (60 min) than this time (Fig. 1). This treatment also failed to inhibit the response when given 2 or 4 hr before testing (not shown).

When tested 30 min after administration, a dose of 20 mg/kg of cimetidine did not block hindpaw FSIA, whereas both the 100 and 200 mg/kg doses of drug significantly inhibited the response (Fig. 2). None of the doses studied changed the analgesic responses in the absence of footshock (Fig. 2).

The ability of cimetidine to inhibit analgesic responses elicited by different amounts of footshock was also studied. As previously shown, cimetidine (100 mg/kg) significantly inhibited the FSIA elicited by 4 mA without affecting the responses in the absence of footshock (Table 1). However, higher currents of footshock (5 and 6 mA) completely surmounted the cimetidine antagonism (Table 1).

Brain and blood levels of cimetidine were measured after peripheral administration of isotopically labeled drug. Thirty min after 100 mg/kg, the levels were 1.95±0.24 nmols/g and 116.5±5.3 μmols/l for whole brain and blood, respectively, yielding a brain/blood ratio of 0.017 (n=5). The respective percentages of radioactivity represented by unmetabolized cimetidine were 65.9±3.2% and 69.1±2.6%.

DISCUSSION

Our hypothesis that brain HA is a mediator of non-opiate FSIA rests in part on the premise that the H_2-antagonists cimetidine, ranitidine and oxmetidine act by inhibiting brain H_2-receptors [13]. We have previously argued that this is likely to be the case because different chemical classes of H_2-blockers are unlikely to share non-H_2-side effects. Although the dose of cimetidine required to inhibit non-opiate FSIA (100 mg/kg, Fig. 2) is large compared to doses that effectively block peripheral H_2-receptors [7], our measurements of brain cimetidine levels after this dose show that (a) cimetidine *does* penetrate rat brain after 100 mg/kg (IP) and (b) brain cimetidine levels after this dose are sufficient to block brain H_2-receptors (but by no means excessive).

Although cimetidine has been shown to penetrate the central nervous system of humans [20] and dogs [28], the ability of this drug to enter the brain of rodents has not been previously demonstrated. Initial autoradiographic studies of peripherally administered cimetidine in rat showed no drug in brain [6], but the dose used was undisclosed. In healthy humans taking multiple doses of cimetidine, cerebrospinal fluid (CSF)/serum ratios were about 0.18, with substantially higher values determined in patients with disease [20]. Consistent with the latter, brain/serum levels in patients having died during cimetidine therapy approached unity [20]. In another study [14], cimetidine was detected in the CSF of patients receiving a single IV dose of cimetidine, but with a mean CSF/plasma ratio of 0.03. In a study of the penetration of cimetidine into dog brain [28], mean CSF/serum ratios were 0.125 after a single IV dose. The brain/blood ratio found presently in rat after a single IP dose (0.017) is similar to the CSF/plasma value found in man after a single dose (0.03) [14] and substantially lower than the CSF/serum value found after a single dose in the dog (0.125) [28]. Colboc *et al.* [5] showed that doses of 50 mg/kg or greater of cimetidine (IP) were required to inhibit the hyperthermic effect of centrally-administered histamine, and suggested that these doses were required to penetrate the rat brain. Our present findings demonstrate direct support for this suggestion.

Without knowing the steady state HA levels immediately around the relevant H_2-receptors, it is impossible to know the precise degree of H_2-antagonism produced by 100 mg/kg cimetidine. However, brain cimetidine levels after this dose (about 2 μM, see Results) exceed the dissociation constant of cimetidine for brain H_2-receptors (0.6 μM) [7], indicating that as many as 77% of otherwise unoccupied brain H_2-receptors may be blocked by this treatment (see [22]). Although our whole brain cimetidine levels indicate the drug's penetration into brain, it should be pointed out that some brain areas may be devoid of drug, whereas other areas lacking a blood brain barrier could have higher cimetidine levels.

Levels of cimetidine in brain 30 min after 100 mg/kg may be the threshold for blocking the hindpaw FSIA. In preliminary studies, we found that brain levels of cimetidine *1 hr* after 100 mg/kg (a treatment found to be ineffective on the FSIA, Fig. 1) are about 1.5 μM, lower than the mean levels achieved after 30 min (1.95 μM). Although this is only a small difference and requires further validation, the finding also seems to explain why cimetidine (100 mg/kg) is only inhibitory at one time after its administration (30 min). Although the pharmacokinetics of cimetidine have not been studied in the rat after IP administration, after a single IV dose, it is distributed according to a two-compartment model, with an elimination half-life of 53 min, and achieves effective antagonism of gastric H_2-receptors for 1–2 hr [2]. In a related preliminary experiment, brain levels of cimetidine 30 min after 20 mg/kg (also ineffective on FSIA, Fig. 2) were about 6-fold lower than those achieved by 100 mg/kg.

We also found that hindpaw FSIA was blocked by

cimetidine, whereas higher currents rendered an analgesic response that was unaffected by the cimetidine treatment (Table 1). This surmountable antagonism is consistent with the known mode of action of cimetidine on H_2-receptors [7], but higher currents could also be recruiting additional mediators that are not blocked by cimetidine. Our earlier findings [13] that a combination of naloxone and cimetidine do not abolish FSIA also suggest the presence of additional mediators.

A brain site of action for cimetidine in inhibiting FSIA predicts that cimetidine administered directly into brain should block the response. Glick and Crane [9] found that HA administered into rat periaqueductal grey caused an analgesic response that was blocked by cimetidine and mimicked by the H_2-agonist dimaprit (see below), both given into the same area. These observations suggest that H_2-receptors in this brain area are capable of producing analgesia.

However, other studies seem at odds with the H_2-analgesia hypothesis. For example, cimetidine (50 μg, administered into the lateral ventricle) had no effect on the non-opiate analgesia elicited by 3 min of AC footshock (2.5 mA) applied to all paws [16]. Although it is not clear that the analgesia measured by these workers is the same as that studied presently, they may be similar, since both are resistant to opiate antagonists [13,16] and both are inhibited by alpha-fluoromethylhistidine (aFMH, see [16] and our unpublished observations), the inhibitor of HA synthesis [8]. Another study [17] found that even higher doses of cimetidine (100–200 μg, given intraventicularly) *produced analgesia* in the absence of footshock. Although these findings must be resolved in terms of our hypothesis, they do not invalidate it. First of all, the present findings suggest that brain cimetidine levels on the order of a *few nanomoles/g* may be sufficient to block FSIA, whereas the workers from the above studies [16,17] probably achieved brain levels of *several hundred* nanomoles/g. Thus, the effect of much lower doses of cimetidine administered into brain should be studied. Secondly, histaminergic fibers in different brain areas may have opposing influences on nociceptive responses. For example, although HA caused analgesia when administered into dorsal raphe, it caused *hyperalgia* when administered into *median* raphe [9]. Thus, the outcome of intraventricular experiments could depend on not only the dose of drug, but also the sites that are reached by a particular route of administration. Intraventricular injections of large doses of cimetidine may also inhibit presynaptic receptors [1], with the net result of *enhancing* histaminergic antinociception, consistent with our hypothesis.

Our use of the hindpaw shock paradigm to produce non-opiate analgesia follows from the work of Watkins *et al.* [26], who suggested that the body region shocked is critical in the production of opiate and non-opiate anaglesia. That is, it was shown that shock applied to front and back paws caused opiate and non-opiate analgesia, respectively. More recently, Cannon *et al.* [3] confirmed these findings, but also found in their laboratory that both types of analgesia can be elicited after shocking either front or back paws, depending on the current and time parameters of the shock. Thus, while there is little doubt that hindpaw footshock can elicit non-opiate analgesic responses [3, 13, 26], the absolute specificity of the body region being shocked is not certain. Non-opiate analgesia also results from AC shock (2.5 mA) applied to all paws for 3 min or greater [24], and this response resembles the hindpaw FSIA in a number of respects. Both analgesic responses probably contain a histaminergic component.

A recent study of FSIA [4] reported an inability to produce naloxone-insensitive analgesic responses, except under conditions that caused damage to the tail. Our studies clearly show that non-opiate FSIA is not an artifact related to tail damage, because H_2-blockers and aFMH block the response. In other words, the apparent "analgesia" that would result from the inability of the tail to sense heat should not be antagonized by any drug.

Our hypothesis predicts that compounds able to stimulate H_2-receptors in brain should have analgesic properties, and is consistent with observations that the H_2-agonist dimaprit causes analgesia when administered into periaqueductal grey [9] or into lateral ventricles [17]. Like HA, dimaprit is highly ionized at physiological pH, and thus would not be expected to penetrate the brain [7]. These findings suggest that derivatives of dimaprit or HA capable of brain penetration should produce analgesia independent of opiate receptors.

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