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Mechanisms of Chloroquine-Induced Body-Scratching Behavior in Rats: Evidence of Involvement of Endogenous Opioid Peptides

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ONIGBOGI, O., A. A. AJAYI AND O. E. UKPONMWAN. *Mechanisms of chloroquine-induced body-scratching behavior in rats: Evidence of involvement of endogenous opioid peptides.* PHARMACOL BIOCHEM BEHAV **65**(2) 333–337, 2000.—Chloroquine is commonly used in the chemotherapy of malaria fever, and as an antiinflammatory disease-modifying agent in patients with rheumatoid arthritis or systemic lupus erythematosus. Administration of chloroquine (20.0 mg/kg IP) significantly ($p < 0.05$) increased the frequency of body scratching in rats to 29.5 ± 9 in 30 min, compared to saline control animals (6.5 ± 2/30 min). Morphine, a μ-opiate receptor agonist (1.0 mg/kg IP), potentiated the chloroquine-induced rat body scratching to 40 ± 6.6, while the μ-opiate receptor antagonist, naltrexone (0.25 mg/kg, IP, given15 min prior) blocked the chloroquine induced body scratching to 4.5 ± 2 ($p < 0.05$ ANOVA). In addition, the frequency of chloroquine (20.0 mg/kg IP)-induced body scratching was significantly reduced to 9.1 ± 3 in 30 min in rats rendered tolerant to morphine ($p < 0.05$ ANOVA) compared to the scratching frequency of 40 ± 6.6 in morphine-naive rats. These suggests an involvement of μ-opioid receptors and/or endogenous opioid peptides in chloroquine induced body scratching in rats. Promethazine, a histamine-receptor antagonist (1.0 mg/kg IP, given 15 min prior to chloroquine) and the corticosteroid, dexamethasone (1.0 mg/kg, IP, given 15 min prior) separately and significantly ($p < 0.01$) inhibited the chloroquine-induced scratching in rats, in a similar manner to clinical studies in malaria. Collectively, the novel results implicate opioidergic mechanisms, and confirm the efficacy of antihistamine and corticosteroids in chloroquine body scratching in rats. It also strongly suggests that the chloroquine-induced body-scratching behavior in the rat may be a useful experimental model for chloroquine-induced pruritus in humans. © 2000 Elsevier Science Inc.

Chloroquine Rats Convulsions Pruritus Opioids Dexamethasone Naltrexone

PRURITUS or itch is a cutaneous sensation that leads to body scratching. Chloroquine is used both as an antimalarial drug and in the treatment of rheumatological disorders, such as rheumatoid arthritis and systemic lupus erythematosus. Chloroquine, however induces a severe generaralized pruritus in up to 70% of adult Africans receiving the drug for the chemotherapy of malaria (4,21). This pruritogenic effect of chloroquine is associated with a reduction in the acceptability and compliance with chloroquine (17). It may also contribute to the emergence of chloroquine resitant strains of *Plasmodium falciparum*, and hamper effective public health control of malaria (17). Chloroquine also causes a troublesome aquagenic-type pruritus, in Caucasian patients treated for rheumatological diseases (15).

The mechanisms of the pruritogenicity of chloroquine are not fully understood (20). However, there is clinical evidence of a pharmacogenetic contribution (4,19), a role for malaria parasitemia (3), as well as the clinical efficacy of corticosteroids (1,3,5,8). Histaminergic mechanisms appear to contribute, but are by no means the sole agents (11,22), and no evidence for an alteration in 12-lipoxygenase pathway following chloroquine dosing, was found in a preliminary study (7).

A major limitation in the study of pruritus in general, is the paucity of suitable animal models (12). In our present study we explored the possible suitability of using the rat body-scratching (BS) behavior as a model to assess the pruritogenic actions of chloroquine, as well as to study its possible mechanisms. It is established that grooming and stereotypic

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behavior patterns in animals are affected by narcotic antagonists (10,24,26,27). We, therefore, specifically examined the hypothesis that endogenous opioid peptides contribute to chloroquine induced rat body-scratching activity. The study also explored the actions of an antihistamine and a corticosteroid commonly used clinically as an antipruritic agent, in the rat body-scratching paradigm.

METHOD

The experiments were carried out using male albino rats (Vom strain), weighing between 150–200 g. They were housed in groups of five rats per cage (40 × 20 × 20 cm). All the animals were housed in a quiet room, under natural lighting and ambient temperature of 26 ± 1°C. Food and drinking water were available ad lib.

ASSESSMENT OF BEHAVIORAL CHANGES

A total of about 80 rats were used in the studies. The rat body-scratching activity was assessed as part of novelty-induced behavior, and was evaluated by placing the animals directly from home cages into a transparent plexiglass cage (45 × 25 × 25 cm) containing sawdust. The cage was illuminated by a soft 60-W white bulb. All rats were observed and assessed singly in the Plexiglas cage, after the injection of the test drugs. Each rat was used only once, as previously described (6).

Experimental Protocol and Drug Injection Schedules

The influence of chloroquine, CQ (10, 20, and 40 mg/kg) and saline on rat body-scratching behavior was studied in six rats. The effects of chloroquine (20 mg/kg), administered 15 min after naltrexone (NX), morphine (M), promethazine (PROM), or dexamethasone (DEXM) on body scratching, was studied using five to eight rats each. The effects of naltrexone, morphine, or dexamethasone alone were studied in six rats each. Eight rats were used for the induction of morphine tolerance.

All the test drugs were administered 15 min prior to a chloroquine (20 mg/kg) injection. Naltrexone (0.25 mg/kg alone, and then 15 min prior to chloroquine (20 mg/kg) injection was given). A naltrexone dose of 0.5 mg/kg given prior to chloroquine caused convulsions in three of the rats so administered.

Morphine (1 mg/kg) was administered alone, or again injected 15 min prior to the standard chloroquine injection. Again, morphine was given simultaneously with promethazine (1 mg/kg), both of which were injected via separate syringes, 15 min prior to chloroquine 20 mg/kg. Dexamethasone (1 mg/kg) alone, or injected 15 min before chloroquine (20 mg/kg) injection was also evaluated. All the injections were intraperitoneal (IP). The injections were timed using a stop clock.

Body Scratching

The body-scratching episode was defined as head scratching or body scratching followed immediately by the licking of the paw used in the scratching (27). The approximate duration of a body-scratching episode was about 10 s. The frequency of the episodic scratching was quantified by using a counter and a timer by one of us unaware of the drug combinations administered. The total frequency of the episodic scratching was summed up for each rat and totaled for the initial 30 min of observation time. The frequencies were used in data analysis. Other behavioral effects of the injected drug combinations, such chewing stereotypy, or tonic–clonic convulsions were noted.

Induction of morphine tolerance. The rats were rendered morphine tolerant to assess the impact of the downregulation of μ-opiate receptors on the chloroquine-induced scratching behavior. A repeated-injection procedure was employed. The rats were injected morphine 1 mg/kg intraperitoneally every morning, for 11 days (27). Chloroquine (20 mg/kg) was then injected 15 min after the last dose of morphine on day 11, and behavioral assay undertaken. A control group of five rats rendered morphine tolerant, were injected with saline instead of chloroquine on day 11, and the behavioral assay performed.

Drugs

The following drugs were used: chloroquine phosphate, promethazine hydrochloride, naltrexone hydrochloride, morphine hydrochloride, and dexamethasone. They were dissolved in physiological saline and administered intraperitoneally (IP) as described above.

Data Analysis

All data are expressed as mean ± standard error of the mean. The effects of saline and chloroquine, 10, 20, and 40 mg/kg were compared by one-way analysis of variance (ANOVA). The effect of chloroquine 20 mg/kg was also compared with the other treatment combinations in a separate analysis by one-way analysis of variance. Post hoc unpaired *t*-tests with Boneferroni correction. The null hypothesis was rejected at $p < 0.05$.

RESULTS

The Effects of Chloroquine and Saline

The frequency of body scratching with saline injection was 6.5 ± 1 in 30 min ($n = 6$). Following chloroquine injections (10, 20, and 40 mg/kg), there was a significant increase ($p < 0.05$ ANOVA) in the frequency of body scratching. The dose–response relationship for the chloroquine enhancement of body-scratching activity was bell shaped. The chloroquine 20-mg/kg dose had the greatest pruritogenic effect of 29.5 ± 9.4 ($p < 0.05$). These results are depicted in Fig. 1.

The Effect of Dexamethasone

Dexamethasone (1.0 mg/kg, 15 min prior) did not significantly alter rat basal body-scratching activity (8.8 ± 2.2) compared to the saline control. It, however, significantly attenuated the effect of chloroquine 20.0 mg/kg-induced body scratching to 5.6 ± 2.0 when compared with a chloroquine 20.0 mg/kg value of 29.5 ± 9.4 ($p < 0.001$ ANOVA) (see Fig. 2).

The Effects of Morphine and μ-Opiate Antagonist, Naltrexone

The opiate agonist and antagonist caused statistically significantly different and qualitatively opposite effects on rat body-scratching behavior ($p < 0.001$, ANOVA; Fig. 2). Morphine alone (1.0 mg/kg , 15 min prior) caused no significantly different effect (3.8 ± 2.0)compared to the saline control (Fig. 2). It, however, potentiated the chloroquine induced scratching to 40.0 ± 6.6 in 30 min (Fig. 2) in comparison to the value of 29.5 ± 9.4 seen with chloroquine 20 mg/kg alone (Fig. 1). Naltrexone alone (0.25 mg/kg) (4.0 ± 0.3) did not differ from saline significantly (Figs. 1 and 2), although it was significantly less than chloroquine 20.0 mg/kg alone ($p < 0.01$). Naltrexone (0.25 mg/kg), when administered 15 min before chloroquine 20.0 mg/kg, significantly attenuated the scratching frequency to 4.5 ± 2.1 compared to chloroquine 20.0 mg/kg alone (29.5 ± 9.4; $p < 0.025$). Naltrexone, at a higher dose of 0.5 mg/kg given 15 min

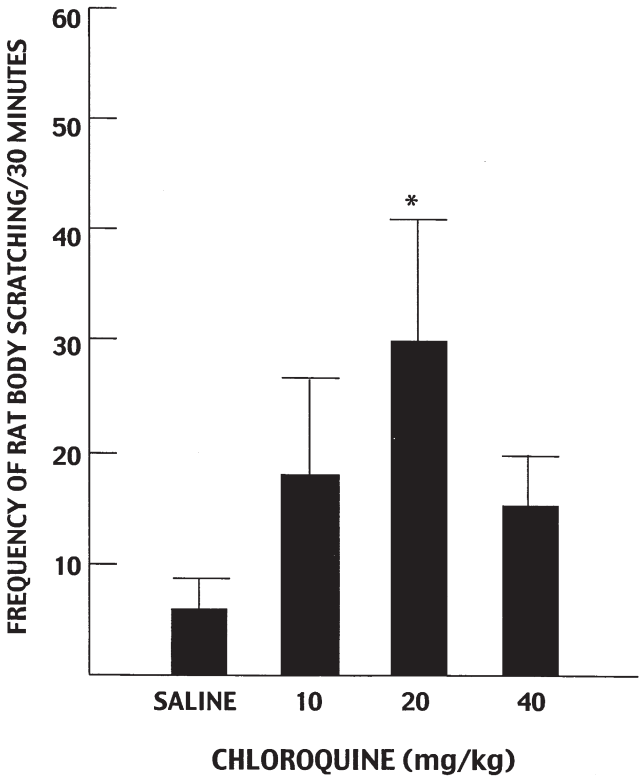

FIG. 1. The effect of chloroquine injections, administered intraperitoneally (IP) at different doses (10, 20, and 40 mg/kg) compared to saline control on the frequency of body scratching over 30 min, in rats ($n = 6$ each). Note the bell-shaped chloroquine dose response. The chloroquine 20.0 mg/kg dose was significantly different.*$p < 0.05$ compared to saline control.

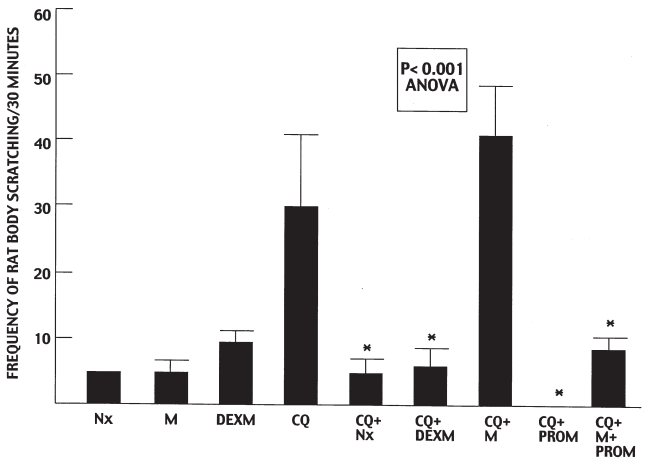

FIG. 2. The effects of intraperitoneal injections of naltrexone, Nx (0.25 mg/kg), morphine, M (1.0 mg/kg), dexamethasone DEXM (1 mg/kg), chloroquine CQ (20.0 mg/kg), promethazine PROM (1.0 mg/kg) alone, or their combinations on the frequency of rat body-scratching activity over 30-min observation times. Evaluation of behavioral effects was commenced immediately after the injections. Where chloroquine was coadministered in combination, it was injected 15 min after the injection of Nx, DEXM, M, or PROM ($n = 5$–8, $p < 0.001$ ANOVA, *$p < 0.05$, **$p < 0.01$, compared to CQ alone).

before chloroquine 20 mg/kg, suppressed the scratching to 5.3 ± 1.9 in three rats; however, in another four rats the combination of Naltrexone 0.5 mg/kg and chloroquine 20.0 mg/kg resulted in abolition of scratching, together with marked stereotypic chewing, a frozen stare that was followed by full-blown tonic–clonic convulsions lasting about 15 s . All the rats fully recovered; there was no mortality.

The Effects of Chloroquine in Morphine-Tolerant Rats

Chloroquine (20.0 mg/kg) induced significantly less body scratching of 9.1 ± 3.1 ($n = 8$) in morphine-tolerant rats when compared to its effect in morphine-naive rats (those that never received morphine, but were injected chloroquine 20.0 mg/kg). The difference between the effects of chloroquine in tolerant (9.1 ± 3.1) and naive rats (29.5 ± 9.4) was highly significant ($p < 0.01$). Likewise, morphine administered acutely enhanced chloroquine body scratching to 40.0 ± 6.6, but this effect was significantly different from the attenuation to 9.1 ± 3.1 seen after 11 days of chronic injections ($p < 0.001$). The effect of chloroquine in the morphine-tolerant rats (9.1 ± 3.1) was not different from the effect of saline injection to another group of morphine tolerant control rats (12.8 ± 4.8, $n = 5$).

Other Behavioral Effects: Stereotypy and Convulsions

In three rats that were rendered morphine tolerant, injection of chloroquine 20.0 mg/kg 15 min after the last morphine dose on day 11 resulted in marked restlessness, stereotyped posture, followed by a frozen stare. Ten minutes after the chloroquine injection, they experienced tonic, and then tonic–clonic convulsions lasting 10 to 15 s. All the three animals recovered, and there was no mortality. These animals were excluded from our data analysis, as were the animals that had convulsions with naltrexone 0.5 mg/kg and chloroquine. No rat experienced convulsions after acute morphine, or with naltrexone or chloroquine administered alone.

Effects of Promethazine and Its Interaction With Morphine

Promethazine (1.0 mg/kg) given 15 min prior, completely suppressed both basal and chloroquine induced rat body scratching ($p < 0.05$). Coadministration of promethazine with morphine and then chloroquine 20 mg/kg resulted in a residual scratching of 8.3 ± 1.8 (see Fig. 2).

DISCUSSION

An interesting and novel finding of our work is the implication of endogenous opioid peptides as a mediator of chloroquine-induced body scratching in rats. Chloroquine (20.0 mg/kg) significantly increased rat body scratching frequency fourfold to 29.5 ± 9.4, in comparison to saline with a frequency of 6.5 ± 1.1 ($p < 0.05$). The dose–response of chloroquine in inducing increased rat body scratching was not linear, but inverted U-shaped (Fig. 1). A similar bell-shaped curve for both endomorphin- and morphine-induced facial scratching has been described in mice (28). This facial scratching in the mice was abolished by the μ-opiate antagonist, naloxone (28).The similarity to the dose–response characteristics of chloroquine-induced scratching in rats may suggest a similar underlying mechanism.

The chloroquine-induced body scratching was abolished

by naltrexone, a μ-opiate antagonist, while naltrexone itself had no discernible effect on basal scratching activity (Fig. 2). Morphine, a μ-opiate receptor agonist, potentiated the chloroquine enhancement of rat body-scratching behavior. However, chloroquine (20.0 mg/kg), administered to morphine-tolerant rats, elicited a significantly attenuated response in the frequency of rat body scratching of 9.1 ± 1.1, either in comparison to chloroquine alone given to naive rats (29.5 ± 9.4), or with morphine given acutely with chloroquine (40.0 ± 7, $p < 0.01$ ANOVA). The effect of chloroquine in morphine-tolerant rats was not different from the effect of saline administered to the morphine-tolerant rats (12.8 ± 4.8). This is in sharp contrast to the fourfold increase in body scratching induced by chloroquine injected in rats that never received morphine (morphine-naive rats).

Collectively, these observations suggest that chloroquine-induced body scratching in rats involves an enhanced release of endogenous opioids and/or stimulation of μ-opiate receptors (24–26,28). Another possibility is that chloroquine interferes with the metabolism of endorphins, because phosphoramidon—an enkephalinase inhibitor that increases cerebral endogenous opioid levels—causes increased scratching behavior in rats (27). The central sites of chloroquine-induced scratching in rats has not been elucidated by the present study. It is, however, known that microinjection of morphine into the ipsilateral and contralateral rat medullary dorsal horn, causes intense facial scratching (25). Thus, the opioid-mediated chloroquine-enhanced body scratching in rats could conceivably occur at a medullary site.

We observed a proconvulsant action of combined naltrexone (0.5 mg/kg) with chloroquine (20.0 mg/kg) in some rats, and this naltrexone dose also inhibited chloroquine-induced body scratching. Interestingly, a similar proconvulsant effect of chloroquine (20 mg/kg) was observed in some morphine-tolerant rats. Neither chloroquine alone nor nalrexone alone caused convulsions in this study. There is both clinical (2) and animal experimental evidence in mice (18) that chloroquine alone may cause seizures or tonic–clonic contractions. The mechanisms by which chloroquine induces epileptic seizures is unclear. However, our present results provides the first evidence to our knowledge that endogenous opioids may be involved. There was a connection between itching suppression and convulsions, as the rats that convulsed rarely scratched. We believe our findings in this regard raises a hypothesis in need of testing.

The antihistamine, promethazine, also completely abolished both basal and chloroquine induced scratch in this rat model. It has been suggested that chloroquine may cause increased urinary excretion of methylhistamine in humans (11). It is also known that morphine and enkephalins may enhance histamine-induced pruritus (14). To determine if the effects of morphine reflects histamine release, promethazine was coadministered with morphine. In the presence of morphine, the antihistamine attenuated but did not abolish the chloroquine rat body-scratching activity. This observation implies that although histamine may contribute to chloroquine-induced pruritus in this rat paradigm, additional mechanisms are involved.

The corticosteroid, dexamethasone, also significantly attenuated the chloroquine-induced scratching in this study. This is in accord with the prednisolone prevention and palliation of chloroquine pruritus in healthy human subjects (1) and in double-blind studies in patients with malaria fever (3,5). The antipruritic efficacy of dexamethasone raises the possibility that prostaglandins or cytokines (interleukin-2) may mediate pruritus in this rat model (13).

Drugs that are effective in the clinical treatment or prevention of chloroquine pruritus in humans (3,5) were also effective in reducing chloroquine-induced body-scratching in rats. This may suggest that chloroquine-induced body scratching in rats is a useful experimental animal model to study clinical pruritus. A limitation of this study is that pruritus was not quantified with regard to the total duration of itching. Some workers have employed videotaped recordings (10,25) to assess the summation of scratching and other behavior. Our counting was done blind by the same observer throughout, and a strong relationship between the total duration and scratching frequency is very likely.

This study has helped advance the understanding of chloroquine-induced itching, which we suggest is of multifactorial causation (3). Endogenous opioids, histamine, and possibly cytokines are involved. Endogenous opioid peptides have been implicated in pruritus secondary to human hepatic cholestasis (16), and naltrexone suppresses itching in chronic renal failure (23). Our demonstration of a role for opioids in chloroquine-enhanced body scratching in rats makes the μ-opioid system an important mediator of the itching sensation in general. The role of other mediators such as serotonin (9) deserve exploration. Further studies with naltrexone in patients with chloroquine-induced pruritus in malaria fever or rheumatological diseases are indicated.

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