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Effects of Pethidine, Acetylsalicylic Acid, and Indomethacin on Pain and Behavior in the Mole-Rat

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TOWETT, P. K. AND T. I. KANUI. *Effects of pethidine, acetylsalicylic acid, and indomethacin on pain and behavior in the mole-rat.* PHARMACOL BIOCHEM BEHAV **45**(1) 153–159, 1993.—The antinociceptive and behavioral effects of pethidine (10, 20, or 30 mg/kg), acetylsalicylic acid (200, 400, or 600 mg/kg) and indomethacin (20, 40, or 50 mg/kg) in the naked mole-rat was studied in the hot-plate test. Instead of inducing analgesia, pethidine caused a dose-dependent reduction in response latency. Sensorimotor impairment and aggressive behavior were also observed following administration of pethidine (20 or 30 mg/kg). All animals receiving pethidine (30 mg/kg) died following fighting when kept in colony cages. Aggressive behavior and death was prevented by naloxone or by keeping animals in single cages. Acetylsalicylic acid (600 mg/kg) and indomethacin (40 or 50 mg/kg) caused a significant increase in response latency. It is concluded that in the mole-rat pethidine elicits aggression, sensorimotor impairment, and apparent hyperalgesia.

Pethidine NSAIDs Nociception Aggression Sensorimotor impairment Hot-plate test Naked mole-rat

ALL animal species down to the protozoan have an ability to detect and respond to tissue-damaging and aversive environmental stimuli (25). The CNS plays a major role in this important function. It is also involved in the regulation of pain sensitivity. There is little knowledge of the anatomy and physiology of the CNS of the naked mole-rat (6,13). Pain perception and regulation in this fossorial rodent is therefore poorly understood.

The naked mole-rat is a subterranean rodent that exhibits eusociality typical of termites (12,14,19,30). The colony, which consists of 75–80 and sometimes up to 250 individuals (30), has one breeding female that maintains her breeding status through behavioral and chemical mechanisms (14). Naked mole-rats inhabit the hot, dry regions of Kenya, Somalia, and Ethiopia. They live in underground burrows where the humidity (±90%), temperature (30–32°C), and carbon dioxide concentration (0.5–2%) are high and the oxygen concentration (15–20%) low (19,28). This rodent has surprisingly unusual features. It has a high rate of thermal conductance, a low basal metabolic rate, and the poorest capacity for thermoregulation of any known mammal (19,28). It has also been classified as a poikilotherm (30). In addition, this mole-rat lacks the normal mammalian SC fat and sweat glands (13). To conserve water, the naked mole-rat excretes dry fecal pellets and produces scanty, concentrated urine (13).

In a recent study (22), no analgesia in the hot-plate test was demonstrated following IP administration of morphine (10, 20, or 30 mg/kg) in the naked mole-rat. Unexpectedly, the authors observed a naloxone-reversible aggressive behavior and motor hyperactivity after these doses of morphine. Opiates are known to induce potent analgesia in a number of species, including mice and rats (2,16), amphibians (31), and crocodiles (23). In the naked mole-rat, however, nefopam, a centrally acting analgesic with both supraspinal and spinal sites of action (11), induced analgesia in the hot-plate test (22). The marked reduction in stepping latency observed after morphine administration in the naked mole-rat was thought to be due to hyperexcitability and motor hyperactivity (22).

In the present study, the antinociceptive effect of an opioid (pethidine) and two nonsteroidal antiinflammatory drugs (NSAIDs) (acetylsalicylic acid and indomethacin) were assessed in the naked mole-rat using a modified hot-plate test (22). In preliminary experiments, we observed that animals showed aggressive behavior and an impairment of sensorimotor function after pethidine administration, and a study of these two behaviors was also included. The time course of the effects of pethidine and indomethacin was also studied using the hot-plate test.

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METHOD

Animals

Naked mole-rats were obtained from Kathekani in the Machakos district of Kenya. They were transported to the laboratory in Nairobi and housed in colonies of 10–50 animals in plastic cages (45 cm in diameter) covered by nontransparent lids to simulate the dark burrows. Paper towels and/or tissue paper was used as bedding to provide more warmth and to soak urine. The bedding was changed regularly. Animals kept on dirty bedding died after a few days. The room temperature was kept constant at 28.0–29.0°C and light was also controlled such that there was 12 D : 12 L cycle. The experiments were performed during the light period. Animals were fed sweet potatoes and carrots ad lib. No free water was given after it was discovered that animals would not take it from either bottles or Petri dishes.

Mole-rats were allowed to adapt to the laboratory for at least 1 month before the start of the experiments. During this period, animals were carefully handled by the experimenter and were adapted to the nonfunctional analgesiameter. Only physically healthy adult male and female animals were used in the study. At the time of the experiments, the weight of animals was 30–50 g.

Drugs

Pethidine HCl (Roche, England) and naloxone HCl (Endo Laboratories, Garden City, NY) were dissolved in saline (0.9% NaCl), while acetylsalicylic acid (Svaneapoteket, Bergen) and indomethacin (Merck Sharp and Dohme) were dissolved in Tris buffer (0.1 M, pH 7.4–7.5). All drugs were dissolved immediately prior to injection.

Nociceptive Testing

Nociceptive testing was performed using an IITC Inc. Model 35D Analgesiameter, the temperature set at 60 ± 0.5°C (22). A digital thermometer (Termoektro a/s, Type 2105; Serial No. 1296; Sensor Cu-CuNi; Range −100/+400, Norway) was used to determine temperature distribution on the hot-plate surface. The latencies to "licking of the toes" of the hindpaw and "stepping" latencies (22) were recorded. Hindpaw licking latencies were found to be more variable than the stepping latency and the data for licking are therefore not presented. A cutoff time of 120 s was chosen during the experiments (22). Mole-rats that did not respond within 120 s were removed from the hot-plate to avoid damage to the foot pads.

To investigate antinociception, pethidine (10, 20, or 30 mg/kg) and/or naloxone (2 mg/kg), acetylsalicylic acid (200, 400, or 600 mg/kg), and indomethacin (20, 40, or 50 mg/kg) were administered IP 30 min before nociceptive testing on the hot-plate. The time course of effects of pethidine (20 mg/kg) and indomethacin (50 mg/kg) were recorded for 4 or 5 h, respectively, at 30, 60, 90, 120, 180, 240, or 300 min after drug injection. In control experiments, an equal volume of vehicle was used.

Aggressive Behavior and Excitation

The effect of vehicle, pethidine (10, 20, or 30 mg/kg) or pethidine (30 mg/kg) plus naloxone (2 mg/kg) on aggressive behavior was investigated. In animals receiving the combined treatment of pethidine and naloxone, four more booster doses (2 mg/kg) of the latter were given at intervals of 30 min. Animals were kept in their home cage, 10 in each cage, or in single cages as shown in the Results section. Animals were keenly observed and their state of excitability scored (see Table 2 below). Assessment of aggressive behavior and degree of excitation was based upon a visual analog scale of 0–3 as follows: normal, 0; mildly excited, 1; excited and mildly aggressive, 2; hyperexcited and severe aggression, 3. Excited and aggressive animals showed more activity, open mouth gaping, incisor fencing, back treading, batting, and biting. Excitability was scored following sound stimulation with a tuning fork. In colony-caged animals, the number of mole-rats participating in fighting and the wounds on their bodies were counted. The number of dead and live mole-rats was recorded 18 h later.

Sensorimotor Function

Immediately after IP administration of vehicle, pethidine, or pethidine plus naloxone, the naked mole-rats were kept in single cages (30 × 30 × 30 cm) and observed for 4 h. Booster doses of naloxone were given at intervals of 30 min for 4 h. Assessment of sensorimotor function and activity was based upon an arbitrary scale of 0–2 as follows: loss of balance, extensor rigidity, and muscle flaccidity, 0; normal motor activity, 1; hyperactivity, 2. The observations were made between 1000 and 1500 h, a period when animals appeared to be less active. The presence or not of sensorimotor impairment was also recorded.

Statistical Analysis

Statistical analysis was performed by analysis of variance (ANOVA). When comparisons were restricted to two means,

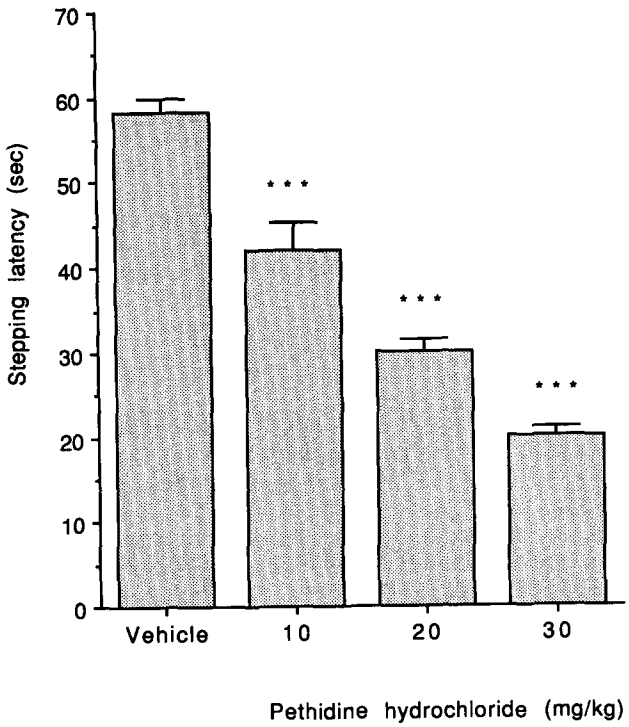

FIG. 1. Effect of IP administration of vehicle or pethidine on stepping latency in the hot-plate test (n = 10 in each group). Data given as mean ± SEM. ***$p < 0.001$, t-test subsequent to ANOVA.

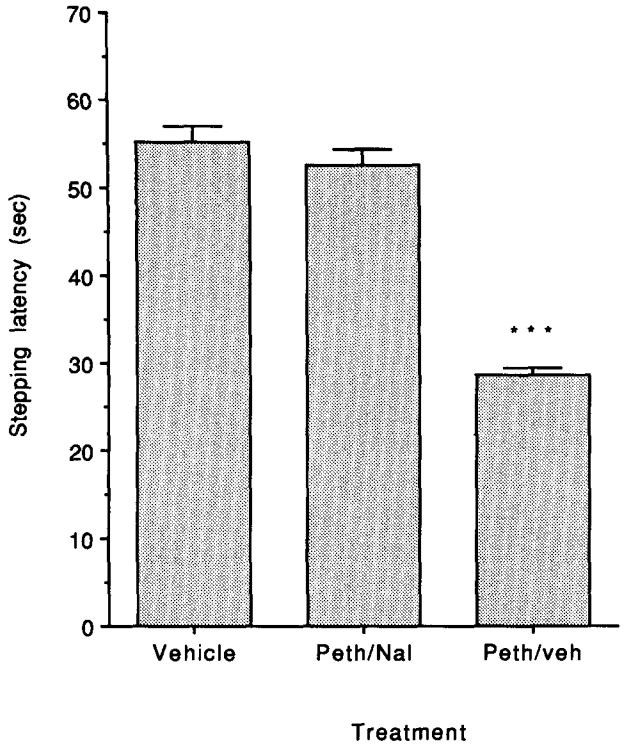

FIG. 2. Effect of IP administration of vehicle, pethidine plus naloxone, or pethidine plus vehicle on stepping latency in the hot-plate test (n = 10 in each group). Data given as mean ± SEM. ***$p < 0.001$, t-test subsequent to ANOVA.

Student's t-test (two tailed) was used. The level of significance was set at 5% ($p < 0.05$). The results are presented as mean ± SEM.

RESULTS

Hot-Plate Test

Pethidine did not induce analgesia; on the contrary, the stepping latency was significantly reduced and in a dose-dependent manner [10 mg/kg, $F(1, 18) = 19.39$, $p < 0.001$; 20 mg/kg, $F(1, 18) = 150.87$, $p < 0.001$; 30 mg/kg, $F(1, 18) = 366.21$, $p < 0.001$]. The stepping latency in vehicle-treated animals was 58.2 ± 1.7 s while in animals treated with pethidine (10, 20, or 30 mg/kg) the stepping latencies were 42.1 ± 3.2, 30.2 ± 1.5, and 20.1 ± 1.0 s, respectively (Fig. 1). Pethidine (5 mg/kg) or naloxone (2 mg/kg) did not significantly influence the stepping latency (data not shown). There was no statistically significant change in the stepping latency following simultaneous administration of pethidine (20 mg/kg) and naloxone (2 mg/kg). The stepping latency in animals receiving the combined treatment was 52.6 ± 1.9 s while in the vehicle-treated group it was 55.2 ± 1.7 s. Injection of pethidine together with vehicle, instead of naloxone, markedly reduced the stepping latency to 28.5 ± 0.2 s, which was statistically significantly different, $F(1, 18) = 139.38$, $p < 0.001$ (Fig. 2).

Acetylsalicylic acid at the lowest doses used (200, 400 mg/kg) failed to cause a significant increase in stepping latency. However, ASA (600 mg/kg) caused a statistically significant elevation of the stepping latency, $F(1, 18) = 6.59$, $p < 0.05$ (Fig. 3). Doses of indomethacin of 40 or 50 mg/kg induced significant increases in stepping latency [40 mg/kg, $F(1, 18) = 5.23$, $p < 0.05$; 50 mg/kg, $F(1, 18) = 9.23$, $p < 0.01$] (Fig. 4). The time course of effects of pethidine (20 mg/kg) and indomethacin (50 mg/kg) are summarized in Figs. 5 and 6, respectively. The reduction in stepping latency was highest 30 min after injection of pethidine. This effect markedly decreased with time and by 180 min the stepping latency was not significantly different from that of vehicle-treated animals. The antinociceptive effect of indomethacin lasted for about 4 h.

Aggressive Behavior

The behavioral changes observed after injection of pethidine are summarized in Table 1. In the colony cages, all naked mole-rats injected with pethidine (20 or 30 mg/kg) participated in fighting. Animals appeared highly excited, most of the time opposing each other in a threatening position and also inflicting small wounds on especially the muzzles and tails of others with their teeth. The number of wounds recorded were dose dependent (Table 1). Eighteen hours after pethidine injection, all naked mole-rats in colony cages receiving 30 mg/kg were dead. None died in the group injected with 20 mg/kg pethidine. Naloxone (2 mg/kg) clearly reduced the aggressive behavior and hyperactivity after pethidine (30 mg/kg). After this combined treatment, none of the animals died during the 14-day observation period. No fighting or wounds were observed. Although some of the animals appeared somewhat hyperactive and excited, the general behavior was clearly more

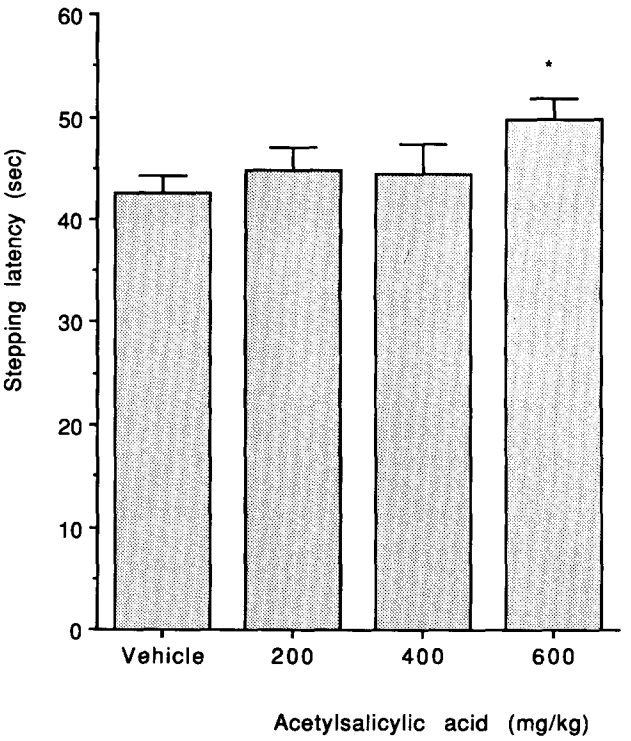

FIG. 3. Effect of IP administration of vehicle or acetylsalicylic acid on stepping latency in the hot-plate test (n = 10 in each group). Data given as mean ± SEM. *$p < 0.05$, t-test subsequent to ANOVA.

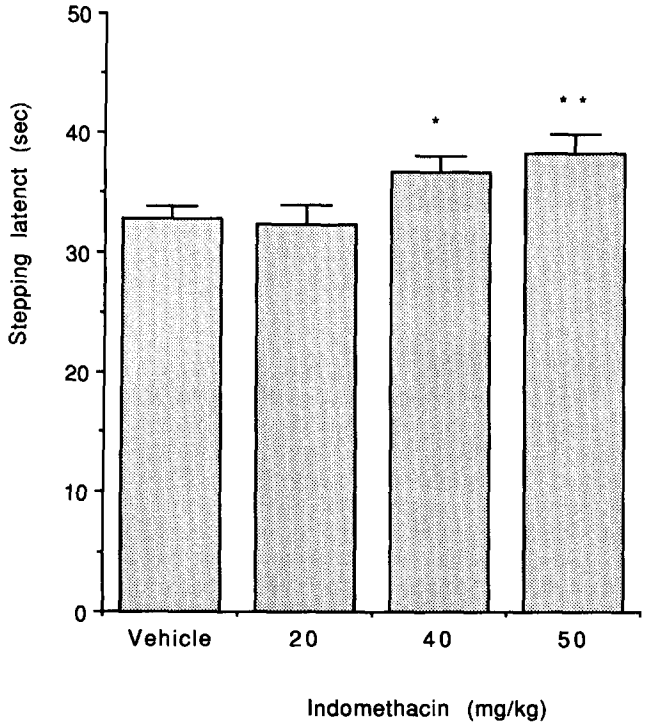

FIG. 4. Effect of IP administration of vehicle or indomethacin on stepping latency in the hot-plate test (n = 10 in each group). Data given as mean ± SEM. $*p < 0.05$, $**p < 0.01$, t-test subsequent to ANOVA.

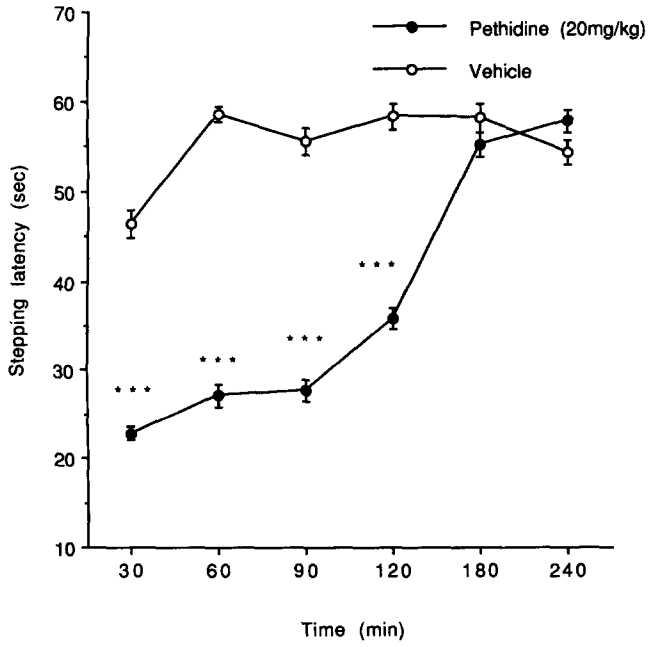

FIG. 5. Time course of the effect of IP pethidine (20 mg/kg) on stepping latency in the hot-plate test (n = 14 in each group). Data given as mean ± SEM. $***p < 0.001$, t-test subsequent to ANOVA.

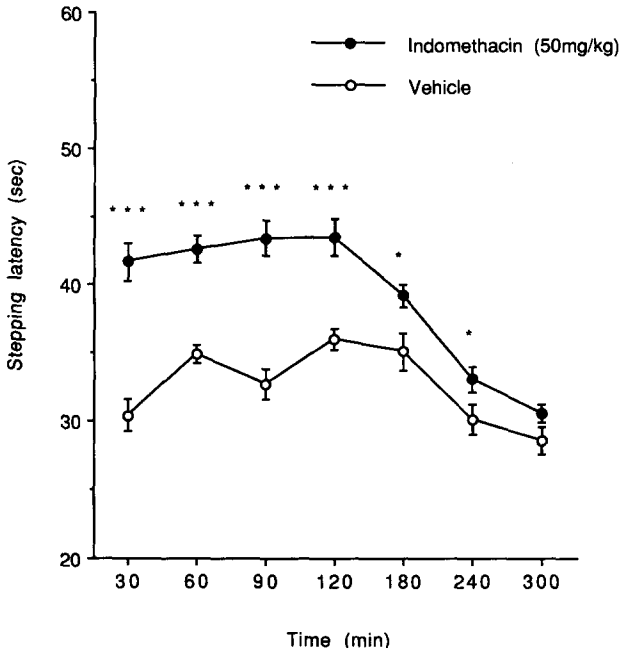

FIG. 6. Time course of the antinociceptive effect of IP indomethacin (50 mg/kg) in the hot-plate test (n = 11 in each group). Data given as mean ± SEM. $*p < 0.05$, $***p < 0.01$, t-test subsequent to ANOVA.

normal than after pethidine only. Naloxone in the absence of pethidine did not significantly alter the behavior.

All naked mole-rats injected with pethidine at 10 mg/kg and kept either in single or colony cages were excited and hyperactive. A similar behavior was also observed in mole-rats injected with pethidine (20 or 30 mg/kg) and kept in single cages. None of the animals, however, died during the 14-day observation period.

Sensorimotor Function

No sensorimotor impairment was observed following administration of pethidine (10 mg/kg). Animals walked normally. However, after injection of pethidine (20 or 30 mg/kg) an initial slight depression of motor activity and, later, excitation was observed. During the phase of depression, there was hypoactivity and sensorimotor impairment. The latter was characterized by loss of balance, extensor rigidity, and muscle flaccidity. Muscle tremors were also observed in affected animals. Sensorimotor impairment occurred 4–10 min after drug injection and lasted for 3–8 min depending upon the dose. After the motor disturbance, animals became highly excited and hyperactive. Animals appeared normal 3 h after drug administration.

Naloxone (2 mg/kg) completely prevented the sensorimotor effects caused by pethidine. Animals appeared more normal after the combined treatment. Table 2 is a summary of motor behavior observed after injection of pethidine or pethidine plus naloxone.

DISCUSSION

Pethidine had no antinociceptive effect in the mole-rat. Morphine has been reported to have an effect similar to this in the hot-plate test in the same rodent (22). Opioid antinoci-

TABLE 1

EFFECT OF VEHICLE, PETHIDINE, OR PETHIDINE PLUS NALOXONE ON MORTALITY AND BEHAVIOR IN THE NAKED MOLE-RAT

Treatment (mg/kg)	*n*	Cage	No. Mole-Rats		
			Fighting	Wounded	Dead
Vehicle	30	Colony	0	0	0
Pethidine 10	10	Colony	0	0	0
Pethidine 10	10	Single	0	0	0
Pethidine 20	10	Colony	10	10 (9.2±0.6)	0
Pethidine 20	10	Single	0	0	0
Pethidine 30	10	Colony	10	10 (41.4±2.0)	10
Pethidine 30	10	Single	0	0	0
Pethidine 30 plus naloxone 2	10	Colony	0	0	0

Mean number of skin wounds in parentheses.

ception has been demonstrated in a wide range of animal species (25,31). Thus, the present finding and the previous report (22) suggest that opioids do not always decrease nociception in animals, as observed in the naked mole-rat. Perhaps this rodent has a peculiar CNS.

An increase in response latency was noted after administration of acetylsalicylic acid (600 mg/kg) or indomethacin (40 or 50 mg/kg). Lower doses of ASA did not have an antinociceptive effect. This is similar to what has been reported in other rodents (2,16,17). This is usually attributed to the insensitivity of the pain test used. It was surprising to demonstrate the antinociceptive effect of indomethacin in this study. Many researchers have failed to demonstrate the antinociceptive effect of this NSAID except in nociceptive tests involving inflammation (17,18). These findings suggest that the naked mole-rat has a nonopioid antinociceptive system sensitive to indomethacin.

Instead of antinociception, pethidine caused a dose-dependent reduction of the stepping latency in the hot-plate test. A similar finding has been reported in the same rodent after morphine administration (22). In the current and previous reports (22), the reduction in stepping latency was clearly naloxone reversible, suggesting that it was mediated via opioid receptors. This reduction in response latency may not necessarily be a sign of hyperalgesia. A hyperalgesic response to opiates occurs after chronic administration (1,27). In this study, animals used were given a single dose of pethidine and had not been previously exposed to any other opioid. An animal's experience on the nociceptive test may result in hyperresponsiveness to noxious stimulation (26,27). Prior to the experiments, animals used in the study had not been exposed to a functional hot-plate.

The cause for the hyperresponsiveness to noxious heat following pethidine administration is not known. This may perhaps be accounted, in part, by hyperexcitability and hyperactivity, which were observed in treated animals. In rats, an increase in pain sensitivity has been observed in those animals with signs of emotional disturbance, such as increased agitation and vocalization (21,33). Perhaps the analgesic effect of pethidine is masked by hyperexcitability in the naked mole-rat. This is an area that requires further investigation.

In the naked mole-rat, doses of pethidine lower than that reported to cause no CNS stimulation in other animals (15) caused marked hyperexcitability and hyperactivity. Hyperexcitability and hyperactivity were even more prominent when lower doses were used. When higher doses were used, a characteristic biphasic response consisting of motor depression followed by motor excitation was observed. This has been reported in other animals also (3,4,20,29,32). It has been suggested that dopaminergic and serotonergic mechanisms are involved in the initiation of the biphasic response in other rodents (7,8,29). Because the opioid system influences behav-

TABLE 2

EFFECT OF IP ADMINISTRATION OF VEHICLE, PETHIDINE, OR PETHIDINE PLUS NALOXONE ON SENSORIMOTOR ACTIVITY IN NAKED MOLE-RATS KEPT IN SINGLE CAGES

Treatment (mg/kg)	*n*	Motor Behavior	
		Motor Impairment	Motor Excitation
Vehicle	30	None	None
Pethidine 10	10	None	Minor activity, mildly excited
Pethidine 20	10	Loss of balance, extensor rigidity/muscle flaccidity	Hyperactivity and hyperexcitability
Pethidine 30	10	Loss of balance, extensor rigidity/muscle flaccidity	Hyperactivity and hyperexcitability
Pethidine 30 plus naloxone 2	10	None	Clearly more normal

ior through interaction with other neurotransmitter systems in the CNS (9), it is possible that the biphasic motor response observed in the naked mole-rat was due to the activation of these systems.

Pethidine also caused a transient motor dysfunction in the naked mole-rat. It has been reported that μ-agonists, even at doses 50 times higher than the analgesic ED_{50}, do not produce detectable motor dysfunction in animals (34). Muscle rigidity and tremors or convulsions have only been reported in mice when large doses of morphine (300 mg/kg) or pethidine (>56 mg/kg) were administered (29). Thus, because low doses of pethidine, a μ-agonist, were used the motor dysfunction observed was unexpected, suggesting that the motor system of the naked mole-rat is readily impaired by pethidine. Naloxone, a blocker for μ-receptors, completely prevented motor dysfunction in the naked mole-rat, suggesting that opioid receptors were involved. A similar motor dysfunction to that induced by pethidine has been reported following exposure of the naked mole-rat to cold (13).

Aggressive behavior was also induced by pethidine in the naked mole-rat. This behavior was due to stimulation of opioid receptors because the blocker for μ-opioid receptors, that is, naloxone, almost completely prevented aggression. These findings together with an earlier study (22) indicate that opioid systems have an important function in the regulation of aggressive behavior in the naked mole-rat. Aggressive behavior in the cat has been reported after morphine administration (5,15). Studies in other rodents and in the cat suggest the involvement of dopaminergic and cholinergic systems in the initiation of aggression (10,24). Perhaps these systems are also involved in the opioid-induced aggression observed in the naked mole-rat. Impairment of memory by pethidine may also partly account for this behavior in the naked mole-rat (9). This is an area that needs further investigation.

Pethidine (30 mg/kg) caused 100 or 0% mortality in naked mole-rats kept in colony or single cages, respectively. Absence of deaths in mole-rats kept in single cages suggests that mole-rats kept in colony cages did not die of toxic side effects caused by pethidine. Further, the number of wounds on the skin of dead animals was very high. Animals died probably following suffocation and hemorrhage.

In conclusion, in the mole-rat and using the hot-plate test stimulation of opioid systems does not cause antinociception but induces sensorimotor impairment and aggressive behavior. The naked mole-rat, however, has an antinociceptive system that can be stimulated by NSAIDs.

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REFERENCES

1. Adams, W. J.; Woods, L. A.; Mitchell, C. L. Drug-test interaction as a factor in the development of tolerance to the analgesic effect of morphine. J. Pharmacol. Exp. Ther. 168:251-257; 1969.
2. Ankier, S. I. New hot-plate tests to quantify antinociceptive and narcotic antagonists activities. Eur. J. Pharmacol. 27:1-4; 1974.
3. Babbini, M.; Davis, W. M. Time-dose relationship for locomotor activity effects of morphine after acute or chronic treatment. Br. J. Pharmacol. 46:213-224; 1972.
4. Bardo, M. T.; Neisewander, J. L.; Enis, R. B. Chronic treatment with naloxone enhances morphine stimulated dopamine neurotransmission: Neurochemical and behavioural evidence. Neuropharmacology 27:1103-1109; 1988.
5. Bowen, J. M. Drugs acting on the nervous system. In: Melby, E. C., Jr.; Altman, N. H., eds. Handbook of laboratory animal science. vol. 3. Cleveland; OH: CRC; 1976:65.
6. Brett, R. A. The ecology and behavior of the naked mole-rat (*Heterocephalus glaber*) Ruppell "Rodentia: Bathyergidae." Ph.D. thesis, University of London, London, UK, 1986.
7. Buxbaum, D. M.; Yarbrough, G. G.; Cater, M. E. Biogenic amines and narcotic effects. I. Modification of morphine-induced analgesia and motor activity after alteration of cerebral amine levels. J. Pharmacol. Exp. Ther. 185:317-327; 1973.
8. Carroll, B. J.; Sharp, P. Monoamine mediation of morphine induced activation of mice. Br. J. Pharmacol. 46:124-139; 1972.
9. D'Amato, R. F.; Castellano, C. Behavioural effects of morphine in mice: Role of experimental housing. Pharmacol. Biochem. Behav. 34:361-365; 1989.
10. Dhasmana, K. M.; Dixit, K. S.; Jaju, B. P.; Gupta, M. L. Role of dopaminergic receptors in maniac response of cats to morphine. Psychopharmacologia 24:380; 1972.
11. Fasmer, O. B.; Berge, O.-G.; Jorgensen, H. A.; Hole, K. Antinociceptive effects of (+/−)- and (+)- and (−)-nefopam in mice. J. Pharmacol. 39:508-511; 1987.
12. Gamlin, L. Rodents join the commune. New Sci. 30 July:40-47; 1987.
13. Hill, W. C. O.; Porter, A.; Bloom, R. T.; Seago, J.; Southwick, D. Field and laboratory studies on the naked mole-rat, *Heterocephalus glaber*. Proc. Zool. Soc. Lond. 128:455-513; 1955.
14. Honeycutt, R. L. Like bees and termites, they cooperate in defence, food gathering and even breeding. How could altruistic behavior evolve in a mammalian species? Am. Sci. 80:43-53; 1992.
15. Hughes, H. C.; Lang, C. M. Control of pain in dogs and cats. In: Kitchell, R. L.; Erickson, H. H., eds. Animal pain, perception and alleviation. New York: American Physiological Society; 1983; 207-216.
16. Hunskaar, S.; Berge, O.-G.; Hole, K. A modified hot-plate test sensitive to mild analgesics. Behav. Brain Res. 21:101-108: 1986.
17. Hunskaar, S.; Berge, O.-G.; Hole, K. Dissociation between antinociceptive and antiinflammatory effects of acetylsalicylic acid and indomethacin in formalin test. Pain 25:125-132; 1986.
18. Hunskaar, S.; Hole, K. The formalin test in mice: Dissociation between inflammatory and noninflammatory pain. Pain 30:103-114; 1987.
19. Jarvis, J. U. M. Energetics of survival in *Heterocephalus glaber* (Rupell), the naked mole-rat. Rodentia: Bathyergidae. Bulletin Carnegie Museum of Natural History, No. 6. Pittsburgh, PA: The Trustees of Carnegie Institute; 1978:81-87.
20. Jorenby, D. E.; Keesey, R. E.; Barker, T. B. Characterization of morphine's excitatory effects. Behav. Neurosci. 102:975-985; 1988.
21. Jørum, E. Analgesia or hyperalgesia following stress correlates with emotional behavior in rats. Pain 32:341-348; 1988.
22. Kanui, T. I.; Hole, K. Morphine induces aggression but not analgesia in the naked mole-rat (*Heterocephalus glaber*). Comp. Biochem. Physiol. 190C:131-133; 1990.
23. Kanui, T. I.; Hole, K. Morphine and pethidine antinociception in the crocodile. J. Vet. Pharmacol. Ther. 15:101-103; 1992.
24. Karczmar, A. G.; Richardson, D. L.; Kindel, G. H. Neuropharmacology and related aspects of animal aggression. Prog. Neuropsychopharmacol. 2:611-631; 1978.
25. Kavaliers, M. Evolutionary and comparative aspects of nociception. Brain Res. Bull. 21:923-931; 1988.
26. Kayan, S.; Woods, L. A.; Mitchell, C. L. Experience as a factor in the development of tolerance to the analgesic effect of morphine. Eur. J. Pharmacol. 6:333-339; 1969.
27. Kayan, S.; Woods, L. A.; Mitchell, C. L. Morphine induced hyperalgesia in rats tested in the hot-plate. J. Pharmacol. Exp. Ther. 177:509-513; 1971.

28. McNab, B. K. The metabolism of fossorial rodents: A study of convergence. Ecology 47:712–733; 1966.
29. Rethy, C. R.; Smith, C. B.; Villarreal, J. E. Effects of narcotic analgesics upon the locomotor activity and brain catecholamine content of the mouse. J. Pharmacol. Exp. Ther. 170:473–479; 1971.
30. Sherman, W. P.; Jarvis, J. U. M.; Braude, S. H. Naked mole-rats. Sci. Am. 267:72–78; 1992.
31. Stevens, C. W. Opioid antinociception in amphibians. Brain Res. Bull. 21:959–962; 1988.
32. Vasko, M. R.; Domino, E. F. Tolerance development to the biphasic effects of morphine on locomotor activity and brain acetylcholine in the rat. J. Pharmacol. Exp. Ther. 207:848–858; 1978.
33. Vidal, C.; Jacob, S. Stress hyperalgesia in rats: An experimental animal model of anxiogenic hyperalgesia in human. Life Sci. 31: 1241–1244; 1982.
34. Yaksh, T. L.; Stevens, C. W. Properties of the modulation of spinal nociceptive transmission by receptor-selective agent. In: Dubner, R.; Gebhart, G. F.; Bond, M. R., eds. Pain research and clinical management. vol. 3. Proceedings of the Vth world congress on pain. Amsterdam: Elsevier Science Publishers, BV (Biomedical division); 1988:417–435.