DR. S. K. MANCHANDA
Professor & Head
Department of Physiology
All India Institute of Medical Sciences
Ansari Nagar, New Delhi-110029.

LETTER TO THE EDITOR

STUDIES ON STARVATION AND DEHYDRATION-INDUCED ANALGESIA IN RATS

Sir,

(Received on September 10, 1981)

Physiological stress is known to induce certain compulsive behaviours like eating, gnawing and licking in animals (6). Physiological stressful situations like immobilisaiton, foot-shock, heat or forced swmming are also known to induce a naloxone–reversible analgesia in animals (1, 2, 3, 4) suggesting involvement of opioid mechanisms. In the present study we have investigated one more type of stress–induced analgesia, namely dehydration analgesia in rats and compared it with starvation–analgesia, feeding and water–drinking both being hypothalamically mediated responses.

Wistar rats of either sex (150–200 *g*) were employed. Each group consisted of a minimum of 5 rats. In food deprivation study, feed, was withdrawn for 24 hr while animals had free access to water. In water deprivation study, water was withheld for 24 hr while animals were given normal feed during the observation period. Analgesia tests were always carried out before noon.

Reaction time to heat was measured with an analgesiometer (4) as a measure of analgesia. The animals were tested after 24 hr of deprivation of food or water alone (control) or after a drug treatment (Table I). Statistical analysis was done using Student's 't' test.

Food or water deprivation for 24 hr significantly increased the pain threshold to heat ($P<0.001$) in comparison to controls. A lower dose of naloxone (1 *mg/kg*) was able to reverse dehydration–induced analgesia whereas a higher dose was needed to reverse starvation–induced analgesia. Chronic deprivation of food or water led to an adaptation phenomenon to stress (Table I) since no analgesia was detected in these groups.

TABLE I : Modification by drugs of analgesia-induced by food- or water- deprivation in rats.

Treatment (mg/kg)	*Mean reaction time sec ± S.E.M.)*			
	n	*Food deprivation*	*n*	*Water deprivation*
Deprivation alone (control)	10	8.0±0.3[a]	47	8.6±0.4[a]
Chronic deprivation (6 days)	5	6.0±0.4**	5	7.0±1.0
Naloxone	5	9.8±0.6	10	3.9±0.3*
(1)		(9.4±0.8)		(6.5±0.6)
(5)	6	7.3±0.5*	—	—
		(10.6±0.4)		
Atropine (1)	8	6.4±1.0 (8.0±0.7)	6	10.5±2.0 (9.2±1.5)
Diazepam (8)	8	3.4±0.4* (6.0±0.46)	5	11.0±0.1 (10.48±0.66)
Propranolol (10)	8	4.6±0.4 (7.0±0.3)	5	8.6±1.0 (8.2±0.37)
Labetalol (10)	6	3.8±0.6* (8.6±1.25)	5	10.0±1.75 (11.1±1.25)
Cyproheptadine (5)	5	3.1±0.16 (5.6±0.83)	5	5.5±0.7** (8.0±0.83)

Drugs were administered intraperitoneally 23.5 hr after deprivation and reaction time to heat was studied after 30 min.

[a]value differ significantly ($P < 0.001$) from normal reaction time 5.05±0.3.

*$P < 0.001$: Value differs significantly from the corresponding value for the control stress group (shown in parantheses).

**$P < 0.01$: Value differs significantly from the corresponding value for control stress group (shown in parantheses).

While pretreatment with beta–adrenoceptor blockers, atropine or diazepam reversed starvation–induced analgesia, pretreatment of animals with these drugs failed to reverse dehydration analgesia. Cyproheptadine, a 5-hydroxytryptamine (5-HT) receptor antagonist, reversed dehydration analgesia but not starvation-analgesia. Treatment with 5-HT depleters (p-chlorophenylalanine, 5, 6-dihydroxytryptamine or fluoxetine) produced reversal of dehydration–induced analgesia (Table II). Quipazine, a 5-HT agonist potentiated the dehydration stress effect.

TABLE II : Modification by serotonergic agents of dehydration-induced analgesia in rats.

Treatment	*n*	*Reaction time (sec±S.E.M.)*	
		Before	*After dehydration.*
Control	6	6.0±0.64	8.6±0.4*
p-Chlorophenylalanine (a)	6	6.0±0.4	6.0±0.4* (8.7±0.6)
5, 6-Dihydroxytryptamine (b)	5	6.6±0.7	6.4±1.4 (8.9±1.1)
Cyproheptadine (5 *mg/kg*, ip)	5	6.0±0.8	5.5±0.3* (8.0±0.8)
Fluoxetine (10 *mg/kg*, ip)	8	—	10.5±1.4 (11.7±1.1)
Quipazine (10 *mg/kg*, ip)	8	6.0±0.5	11.8±0.8* (8.0±0.3)

*$P < 0.001$ as compared to the corresponding stress effect shown in parantheses.

[a]100 *mg/kg/day* was given intraperitoneally for 3 days and animals were used 24 hr later.

[b]75 µg was given intracerebroventricularly 48 hr before.

Like other stress analgesia (1, 2, 3, 4), food- or water- deprivation-induced analgesia also seem to be mediated through endogenous opioid mechanisms as the response was naloxone reversible. The dehydration-induced analgesia, though naloxone reversible, differed from starvation analgesia in view of the drug interactions shown in the Table I. The involvement of putative opiate mechanism in dehydration-analgesia appears to be selectively modulated by 5-HT pathways as substances which deplete brain 5-HT or 5-HT receptor blocker reversed this phenomenon and quipazine augmented the analgesic response. Starvation-analgesia was resistant to such treatment.

ACKNOWLEDGEMENTS

The study was supported by the financial assistance of Indian National Science Academy, New Delhi. The authors thank M/s Endo Laboratories, New York (Naloxone);

Eli Lilly, USA (Fluoxetine); Galaxo, UK (Labetalol) and Merck Sharp & Dohme, USA (Cyproheptadine) for the generous supply of drugs used in the present study.

S. K. KULKARNI AND REJIT K. ROBERT

Pharmacology Division,
Department of Pharmaceutical Sciences,
Panjab University, Chandigarh - 160 014

REFERENCES

1. Akil, H., J. Madden, R.L. Patrick and L.D. Barchas In: Opioids and endogenous opioid peptides by Kosterlitz, H. Amsterdam, Elsevier/North Holland Biomedical Press, p 63, 1976.
2. Bodnar, R.J., D.D. Kelly, A. Splaggia, C. Ehrenberg and M. Glusman. Dose dependant reduction by naloxone of analgesia induced by cold-water stress. *Pharmacol. Biochem. Behav.*, **8** : 667–672, 1978.
3. Kulkarni, S.K. Heat and other physiological stress–induced analgesia : Catecholamine mediated and naloxone reneversible response. *Life Sci.*, **27** : 185–188, 1980.
4. Kulkarni, S.K. Heat stress–induced analgeisa : Non–specific response to stress. *Indian J. Exptl. Biol.*, **19** : 1190–1191, 1981.
5. McGivern, R., C. Berka, G.G. Berntson, J.M. Walker and C.A. Sandman. Effect of naloxone on analgesia induced by food deprivation. *Life Sci.*, **25** : 885–888, 1979.
6. Morley, J.E. and A.S Levine. Stress–induced eating is mediated through endogenous opiates. *Science*, **209** : 1259–1260, 1980.