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Naloxone reduces diuretic responses induced by water, alcohol or congenital lack of vasopressin in rats

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1 The effects of naloxone (2 and 10 mg kg^{-1} s.c.) were compared in several kinds of experimental polyuria: alcohol- or water-loaded rats and Brattleboro rats (i.e. animals with congenital lack of vasopressin).

2 In normal rats, both water and alcohol increased urine flow and decreased urinary osmolality. Alcohol induced a more marked diuretic response than water.

3 In normally hydrated rats, naloxone (2 and 10 mg kg^{-1} s.c.) failed to modify urine flow, urinary osmolality, Na^+ and K^+ urinary excretion, and urine creatinine concentration.

4 The two doses of naloxone decreased urine flow and increased osmolality in both water- and alcohol-loaded rats.

5 In Brattleboro rats, naloxone (10 mg kg^{-1} s.c.) reduced urine flow and urinary creatine whereas the low dose (2 mg kg^{-1} s.c.) was without effect.

6 Since it is well known that the mechanism of water- or alcohol-induced diuresis is an inhibition of vasopressin release, the present results suggest that naloxone could prevent this inhibition. They indicate that endogenous opioid peptides may exert an inhibitory control on vasopressin release.

Introduction

It is now well established that naloxone, an opiate antagonist (Sawynok, Pinsky & Labella, 1979), is able to reduce water drinking and fluid consumption (Holtzman, 1974; Brown & Holtzman, 1979; 1981). However, few reports have discussed the influence of naloxone on urinary flow. Huidobro (1978), Bisset, Chowdrey & Feldberg (1978), Grossman & Besser (1980), Montastruc, Morales-Olivas & Montastruc (1980) found that naloxone *per se* had no diuretic or antidiuretic action in animals or man. In contrast, Vandeputte-Van Messom & Peeters (1980) reported that the injection of naloxone alone into the third ventricle of conscious goats induced both a diuretic response and an increase in free water clearance, whereas Delbarre, Casset-Senon, Delbarre, Sestillange & Christin (1982) found that naloxone elicited a dose-related diuretic response in normotensive but not in spontaneously hypertensive conscious rats.

The antidiuretic action of morphine is well documented (see Fujimoto, 1971) although the mechanism of its effect is still under discussion. De Bodo (1944) first proposed that the antidiuretic effect of morphine was mediated via the liberation of vasopressin from the neurohypophysis. Other studies have suggested that the antidiuretic effects of opiates are seen when associated with haemodynamic changes (Skowsky, Smith & Swan, 1978) and that the primary effect of morphine or β endorphin is to suppress rather than stimulate vasopressin release (Van Wimersma Greidanus, Thody & Verspaget, 1979; Iversen, Iversen & Bloom, 1980; Lutz-Bucher & Koch, 1980).

These conflicting results, and the fact that naloxone was reported to antagonize the behavioural effects of alcohol intoxication (Sørensen & Mattisson, 1978; Jeffcoate, Herbert, Cullen, Hastings & Walder, 1979; Barros & Rodriguez, 1981) led us to study the influence of naloxone on the diuretic responses and urinary parameters elicited by alcohol load (an effect due to an inhibition of vasopressin release: Ames & Van Dyke, 1951; Baïsset & Montastruc, 1962; Cicero, 1981). The results were compared with those obtained in normal rats with water load or in Brattleboro rats with hereditary hypothalamic diabetes insipidus.

Methods

Experiments were performed on male Wistar rats weighing 350 to 400 g and homozygous Brattleboro rats (300–320 g) with hereditary diabetes insipidus caused by congenital lack of vasopressin (Miller & Moses, 1971). During each experiment (4 h), rats deprived of food and water were housed two per metabolic cage.

Normal rats

In normal rats, 9 groups were studied.
(a) *Normally hydrated rats:* Rats treated with saline solution (0.9% NaCl) subcutaneously ($n = 20$); (2) treated with naloxone 2 mg kg^{-1} s.c ($n = 20$) and (3) treated with naloxone 10 mg kg^{-1} s.c ($n = 20$).
(b) *Water-loaded rats:* Rats deprived of food but not water during the night before the experiment received distilled water (temperature: 35°C) equal to 10% of body weight by means of a stomach cannula according to the technique described by Gilman & Goodman (1937). Two loads equal to 5% of body weight each were successively given at times $t = 0$ (first load) and $t = 20$ min (i.e. time necessary for gastric emptying: second load) to three groups of animals: (4) treated with saline s.c. ($n = 20$); (5) treated with naloxone 2 mg kg^{-1} s.c. ($n = 20$) and (6) treated with naloxone 10 mg kg^{-1} s.c. ($n = 20$).
(c) *Alcohol-loaded rats:* Rats deprived of food but not water overnight received by gavage a volume of 10% ethanol (temperature 35°C) equal to 5% of body weight at time $t = 0$ and 20 min later another volume of 5% of body weight of distilled water. Three groups were used: (7) treated with saline s.c. ($n = 20$); (8) treated with naloxone 2 mg kg^{-1} s.c. ($n = 20$) and (9) treated with naloxone 10 mg kg^{-1} s.c. ($n = 20$).

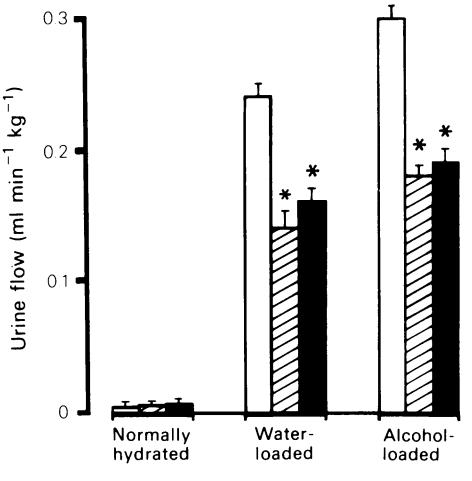

Figure 1 Effects of naloxone on urine flow in normal rats: three groups were studied: normally hydrated rats, water- and alcohol-loaded rats. In each group: first (open) column: 20 rats treated only with saline solution; second (hatched) column: 20 naloxone (2 mg kg^{-1})-pretreated rats; third (solid) column: 20 naloxone (10 mg kg^{-1})-pretreated rats. The results (mean values with s.e.mean) are expressed as ml min^{-1} kg^{-1} of body weight during the 4 h of experiment. The vertical lines represent the s.e.mean. Statistical comparisons, in each group, refer to saline group. *$P < 0.001$

Brattleboro rats

Since these animals have a permanent polyuria, no load was given. Three groups of 30 each were studied: (1) treated with saline s.c. ($n = 30$); (2 and 3) two groups of 30 animals each treated with naloxone 2 or 10 mg kg^{-1} s.c.

Drugs used

Naloxone hydrochloride (Narcan, Winthrop; 2 and 10 mg kg^{-1}) or saline solution were administered subcutaneously at the beginning of the experiment i.e. just before the first load.

Parameters studied

Urine was collected at hourly intervals during the 4 h of experiments for measurement of osmolality, Na^+ and K^+ excretion and urinary creatinine concentration. Osmolality (as mosm kg^{-1} H_2O) was measured by freezing point depression with an osmometer (Advanced Instruments Massachussets). Na^+ and K^+ (as μmol min^{-1} kg^{-1}) were evaluated by flame photometry, and creatinine concentration (mmol h^{-1} kg^{-1}) was determined on a Technicon auto-analyzer. Total urinary volume, measured during the 4 h of experiments for each group of 2 animals was expressed as ml min^{-1} kg^{-1} of body weight.

Statistical evaluations

Results (expressed as mean values ± s.e.mean) were analysed by a two-way analysis of variance followed by a Bonferroni method. The level of significance was $P < 0.01$.

Results

Effects of alcohol or water load

In normal rats, both water and alcohol significantly increased ($P < 0.001$) urine flow (Figure 1), induced a decrease in urine osmolality (−78% for water,

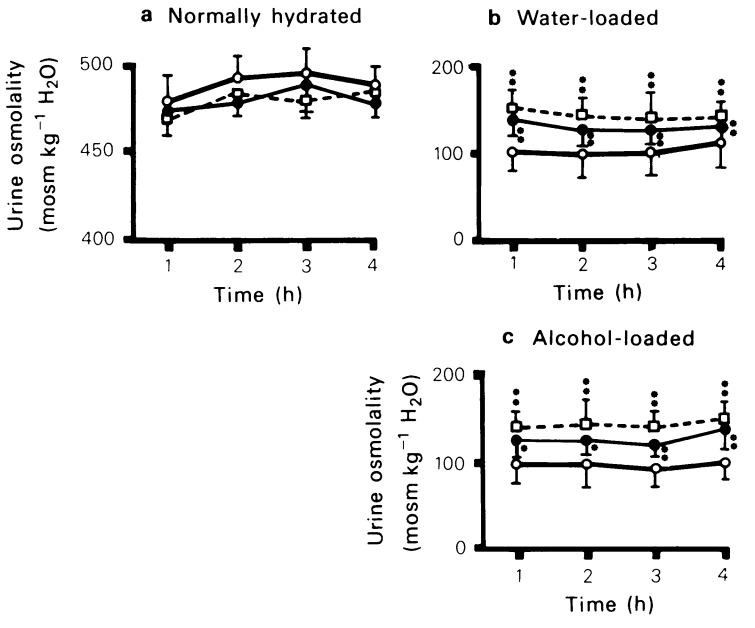

Figure 2 Effects of saline (○), naloxone (□) (2 mg kg^{-1}) and naloxone (■) (10 mg kg^{-1}) injected subcutaneously on urine osmolality in normal rats. Three experimental groups were studied: (a) normally hydrated rats, (b) water-loaded rats, (c) alcohol-loaded rats. Results are expressed as mosm kg^{-1} H_2O. Values shown are mean for 20 animals. The vertical lines represent s.e.mean. Statistical comparisons, in each case, refer to saline group. *P value < 0.01; **$P < 0.001$.

−80% for alcohol) compared with normally hydrated saline-treated rats (Figure 2). Water and alcohol load did not significantly change Na^+, K^+ urinary excretion and urine creatinine concentration compared with normally hydrated rats (Table 1).

Effects of naloxone 2 mg kg^{-1} (s.c.)

In normally hydrated rats, naloxone alone did not change urine flow (Figure 1) and the other studied parameters (Figure 2a, Table 1) compared with con-

Table 1 Effects of naloxone (2 and 10 mg kg^{-1} s.c.) on excretion of urine electrolytes and creatinine concentration in normal rats

Treatment	*Na^+* (μmol min^{-1} kg^{-1})	*K^+* (μmol min^{-1} kg^{-1})	*Creatinine* (mmol h^{-1} kg^{-1})
Normally hydrated			
Saline	0.77 ± 0.07	0.82 ± 0.05	7.68 ± 0.28
Naloxone 2 mg kg^{-1}	0.76 ± 0.08	0.83 ± 0.06	7.22 ± 0.30
Naloxone 10 mg kg^{-1}	0.73 ± 0.08	0.79 ± 0.09	6.96 ± 0.40
Water loaded			
Saline	0.81 ± 0.08	1.23 ± 0.11	8.38 ± 0.24
Naloxone 2 mg kg^{-1}	0.71 ± 0.07	0.85 ± 0.21	7.98 ± 0.42
Naloxone 10 mg kg^{-1}	0.68 ± 0.08	0.92 ± 0.19	7.51 ± 0.33
Alcohol loaded			
Saline	1.34 ± 0.14	1.24 ± 0.24	8.72 ± 0.47
Naloxone 2 mg kg^{-1}	1.37 ± 0.11	1.09 ± 0.15	8.05 ± 0.39
Naloxone 10 mg kg^{-1}	1.41 ± 0.20	1.37 ± 0.16	7.90 ± 0.30

Urine electrolytes measured in a sample obtained over 4 h are expressed as μmol min^{-1} kg^{-1} of Na^+ and K^+, and mmol h^{-1} kg^{-1} of creatinine. Values shown (mean values ± s.e.mean) are mean for 20 animals. Statistical comparisons, in each case, refer to saline group. No significant statistical difference was found between the different groups (level of significance, $P < 0.01$ with Bonferroni test).

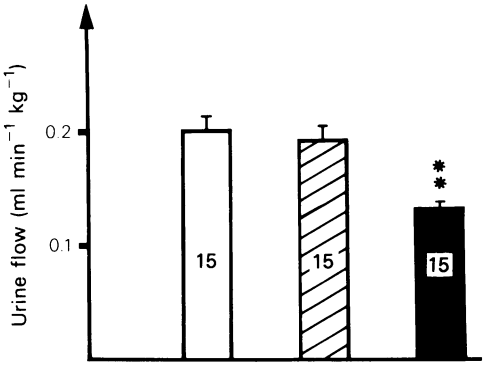

Figure 3 Effects of naloxone (2 and 10 mg kg^{-1} s.c.) on urine flow in Brattleboro rats. Three groups of 30 rats each were studied. Open column: saline (s.c.) treated rats (control); hatched column: naloxone-(2 mg kg^{-1} s.c.) treated rats; solid column: naloxone-(10 mg kg^{-1} s.c.) treated rats. The results (mean values with s.e.mean) are expressed as ml min^{-1} kg^{-1} body weight over 4 h. The vertical lines represent s.e.mean. Statistical comparisons refer to the control group. $^{**}P<0.001$

trol. Naloxone produced a 46% and 48% decrease in urine flow respectively in water- and alcohol-loaded animals (Figure 1) ($P<0.001$ compared with saline-treated rats). The drug increased urinary osmolality (+38% in water-loaded, +33% in alcohol-loaded rats; $P<0.001$) (Figure 2b, c) without changing Na^+ and K^+ excretion and urine creatinine concentration (Table 1).

In Brattleboro rats, this dose of naloxone did not modify polyuria (Figure 3), urine osmolality or electrolyte excretion (Figure 4).

Effects of naloxone 10 mg kg^{-1} (s.c.)

At this higher dose, naloxone did not change urine flow (Figure 1) and the other parameters in normally hydrated rats (Figure 2a, Table 1). Administration of naloxone reduced water- or alcohol-induced polyuria (−35% and −45% respectively; $P<0.001$) (Figure 1), increased urine osmolality (+22% in water-loaded, +28% in alcohol-loaded rats; $P<0.001$, Figure 2b, c), but did not change the values of Na^+ and K^+ excretion and creatinine (Table 1). In Brattleboro rats, naloxone reduced diuresis (−35%; $P<0.001$ compared with control Brattleboro animals) and did not change urine osmolality or levels of electrolytes (Figure 4a, b, c). However the opiate antagonist significantly ($P<0.01$) decreased urinary creatinine concentration (Figure 4d) compared with control saline-treated Brattleboro animals.

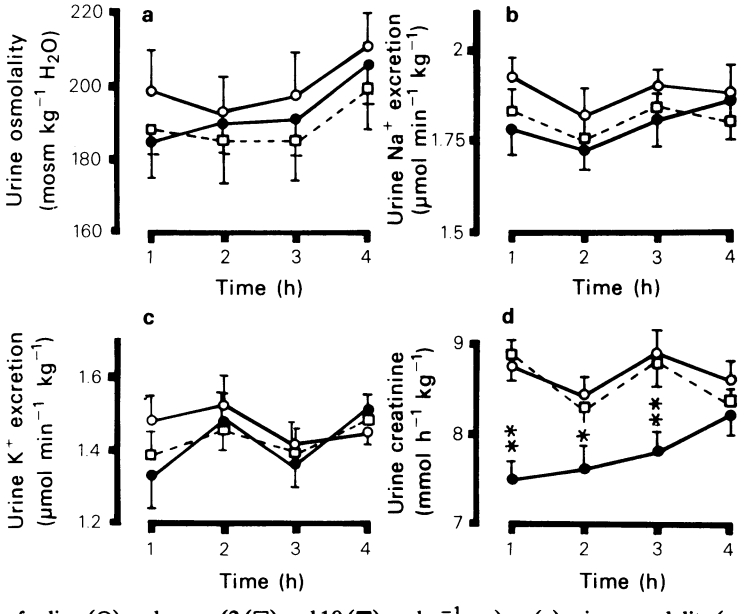

Figure 4 Effects of saline (○), naloxone (2 (□) and 10 (■) mg kg^{-1} s.c.) on (a) urine osmolality (mosm kg^{-1} H^2O); (b) Na^+ excretion (μmol min^{-1} kg^{-1}); (c) K^+ excretion (μmol min^{-1} kg^{-1}) and (d) urine creatinine (mmol h^{-1} kg^{-1}) in Brattleboro rats. Values shown are mean of 30 animals; vertical lines show s.e.mean. Statistical comparisons in each case, refer to saline group. $^{*}P<0.01$; $^{**}P<0.001$.

Discussion

The present data show that naloxone alone, which is inactive in normally hydrated rats, is able to induce both a decrease in urine flow and an increase in urine osmolality in alcohol- or water- replete rats without any change in electrolyte or creatinine excretion. It is well known that both water and alcohol loads induce diuresis by inhibition of vasopressin release (for reference see Baïsset & Montastruc, 1976; Cicero, 1981) and it is suggested that naloxone could prevent this inhibition of vasopressin release.

Since naloxone can be used to provide indirect evidence for the release of opiate peptides (Akil, Madden, Patrick & Barkas, 1976; Dashwood & Feldberg, 1980), the present results showing an antidiuretic action of naloxone without urinary Na^+ and K^+ change suggest that endogenous opiates may exert an inhibitory control on vasopressin release, at least under our experimental conditions. The fact that naloxone alone ($2\ mg\ kg^{-1}$) failed to modify polyuria in Brattleboro rats agrees with this conclusion. However, it should be noted that the higher dose ($10\ mg\ kg^{-1}$) of naloxone decreased urine flow and urinary creatinine concentration in these animals deprived of vasopressin secretion. To explain this unexpected result, one can suggest that this dose of naloxone could decrease the glomerular filtration rate as suggested by the decrease in urine creatinine concentration.

The hypothesis of an inhibitory influence of endogenous opiates on vasopressin release agrees with recent biochemical data obtained after direct measurement of vasopressin levels; Van Wimersma Greidanus *et al.* (1979) found that morphine or β endorphin lowered plasma arginine vasopressin levels after peripheral or intracerebroventricular administration in rats. Iversen *et al.* (1980) showed that an enkephalin analogue, as well as morphine or β-endorphin, inhibits the release of vasopressin evoked by electrical stimulation of the rat pituitary stalk *in vitro*. This inhibition can be reversed by naloxone. Using incubated neurointermediate lobe and pars nervosa of rat pituitary, Lutz-Bucher & Koch (1980) found that naloxone reversed the inhibitory action of morphine or endorphins on hormonal output. Knepel, Nutto, Anhut & Hertting (1980) demonstrated that naloxone enhanced the isoprenaline-induced increase in plasma vasopressin concentration in conscious rats. Lightman, Langdon, Todd & Forsling (1982) found that naloxone increased both the plasma vasopressin response to nicotine and the resulting rise in urine osmolality in man. They suggested that opioid inhibition of vasopressin secretion occurred only when the secretory system was stimulated and did not affect basal release. This conclusion agrees with our present findings. Clarke, Lincoln & Wood (1980) showed that a low dose of morphine injected intraventricularly inhibits the activity of vasopressin neurones. The occurrence of hypothalamic enkephalin neurones projecting to the pars nervosa and regulating neurohypophysial secretion was also reported by Rossier, Battenberg, Pittman, Bayon, Koda, Miller, Guillemin & Bloom (1979).

However, some data suggest a more complex action of endogenous opioids on vasopressin release: Millet, Conte-Devolx, Giraud, Gillioz, Tognetti & Oliver (1979) reported that naloxone did not change plasma values of arginine vasopressin in dehydrated rats. More recently, Knepel, Nutto, Anhut & Hertting (1982) suggested that this inhibitory control by endogenous opiates is involved in some but not all of the different pathways leading to vasopressin release.

From a therapeutic point of view, our results suggest that naloxone may be a useful drug in the treatment of alcohol withdrawal in man, not only in order to antagonize the central behavioural effects (Myers, 1978) of alcohol (for reference see introduction) but also to reduce polyuria and polydipsia induced by alcohol dependence by an action on vasopressin release. Such an interaction between naloxone and alcohol has been described previously: the drug has been reported to antagonize ethanol-induced narcosis in mice, the central depression produced by a combination of barbiturates, alcohol and diazepam in humans, and the effects of both alcohol and chlordiazepoxide on self-stimulation behaviour in rats (for review see Blum, Hamilton & Wallace, 1977; Myers, 1978). Boada, Feria & Sanz (1981) also demonstrated an inhibitory action of naloxone on ethanol-induced antinociception in mice. Recently, Hiller, Angel & Simon (1981) found that alcohol inhibits binding to delta opiate receptors.

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