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Endocrine Effects of Ethanol Infusion in Normal Subjects: Modification by Naloxone

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JEFFCOATE, W. J., P. PLATTS, M. RIDOUT, A. G. HASTINGS, I. MACDONALD AND C. SELBY. *Endocrine effects of ethanol infusion in normal subjects: Modification by naloxone.* PHARMAC. BIOCHEM. BEHAV. **13**: Suppl. 1, 145–148, 1980.—The intravenous infusion of ethanol (1 mg/kg over 30 min) in four normal females produced no clear change in circulating levels of plasma cortisol, corticotrophin, prolactin and growth hormone. The simultaneous infusion of naloxone (2 mg/hr over 90 min) and ethanol caused a rise in cortisol, corticotrophin and prolactin whereas levels of growth hormone remained low. It is argued that some of the endocrine effects of ethanol may be mediated via central opiate receptors.

Ethanol Naloxone Opiate receptors Endorphin Cortisol Corticotrophin Prolactin Growth hormone

BOTH the acute and chronic administration of ethanol have widespread effects on the endocrine system in man [5]. Since many of the endocrine effects of ethanol abuse resemble those of opiate addiction, it is possible that the mechanisms involved are similar and that ethanol may interact indirectly with opiate receptors. Two alternative mechanisms have been postulated for such interaction: a. that acetaldehyde derived from ethanol reacts with dopamine *in vivo* to generate alkaloids capable of binding to opiate receptors [2], and b. that ethanol may modify the release of endogenous opioid peptides, enkephalins and endorphins [3]. In either instance the effects of ethanol may be blocked by the administration of an opiate receptor antagonist, such as naloxone. In the present study we report the effects of naloxone on the endocrine changes induced by the intravenous infusion of ethanol in four healthy women.

METHOD

Four female volunteers (age 23–25) were studied on each of four test days. Two subjects (nos. 1 and 4) were taking an oral contraceptive pill. Studies followed 24 hr abstention from alcohol and a 3 hr fast, and were completed between 1300 hr and 1800 hr on each test day. Test days were separated by at least one week. Each subject acted as her own control and received four separate infusions in random sequence: ethanol alone, naloxone alone, ethanol plus naloxone and saline control (Fig. 1). Ethanol (1 ml/kg diluted to 500 ml with normal saline) was administered by intravenous infusion through a heating coil at 37°C, over 30 min between time 60 and 90 min. On control days 500 ml normal saline was infused in place of ethanol. Naloxone (NARCAN, Winthrop Ltd, 4 mg diluted in 24 ml saline) or normal saline was infused into the opposite arm at a rate of 12 ml/hr (2 mg/hr naloxone for 90 min between time 30 and 120 min). Naloxone and saline were administered single blind. Blood sampling was performed each 30 min via a 3-way tap kept patent by a slow intravenous infusion of normal saline (100 ml maximum volume in 3 hr). Samples were analysed by radioimmunoassay for cortisol (Amerlex, Radiochemical Centre, Amersham), corticotrophin (ACTH) [7], prolactin (PRL) (C.I.S., U.K. Ltd.), growth hormone (GH) (U.K. Supraregional Assay Service reagents; iodinated GH from C.I.S., U.K. Ltd.). Alcohol was assayed by the alcohol dehydrogenase method [1].

RESULTS

Cortisol (Figure 2)

A rise in plasma cortisol following ethanol alone was seen in only one subject. The combination, however, of ethanol and naloxone produced a clear rise in three subjects. The administration of naloxone alone showed no consistent effect, and on the saline control day levels of cortisol fell steadily in all four subjects (not illustrated).

ACTH

Levels of plasma ACTH paralleled those of cortisol closely, although peaks of ACTH preceded those of cortisol, as expected. Results for all four infusions in subject 3 are illustrated in Fig. 3.

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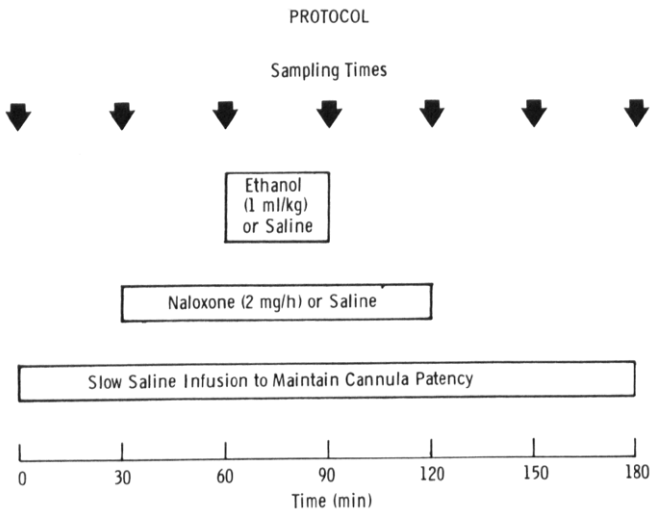

FIG. 1. Test protocol. Naloxone (2 mg/hr) or an equivalent volume of normal saline was infused, double-blind, between time 30 and 120 min. Ethanol (1 ml/kg) diluted to 500 ml with normal saline, or normal saline, was administered between time 60 and 90 min in the opposite arm.

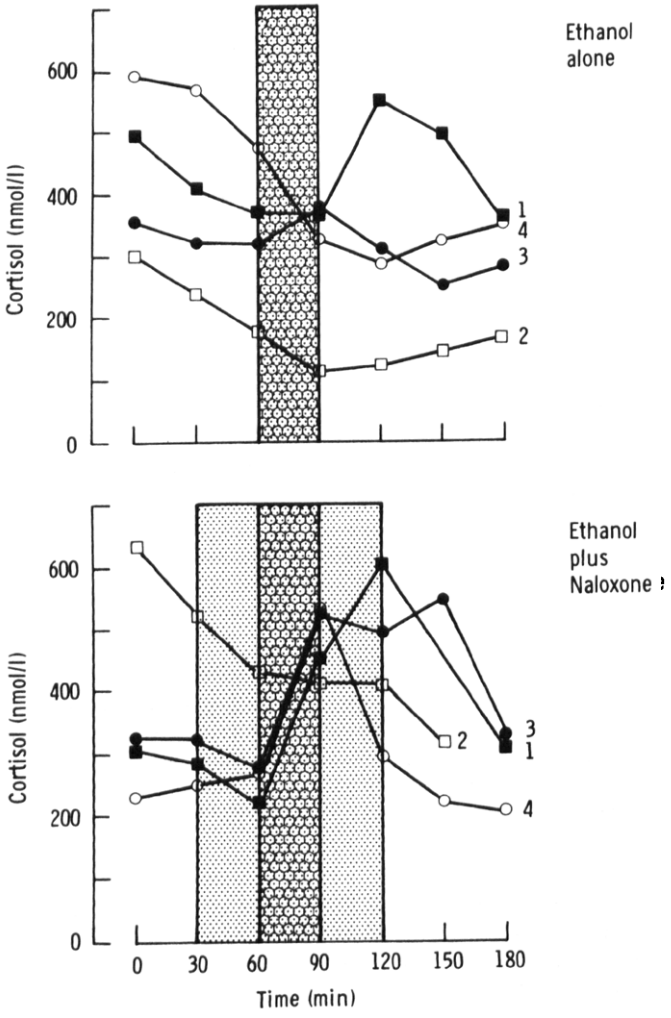

FIG. 2. Effect of ethanol infusion (1 ml/kg in 500 ml normal saline), alone or combined with naloxone infusion (2 mg/hr).

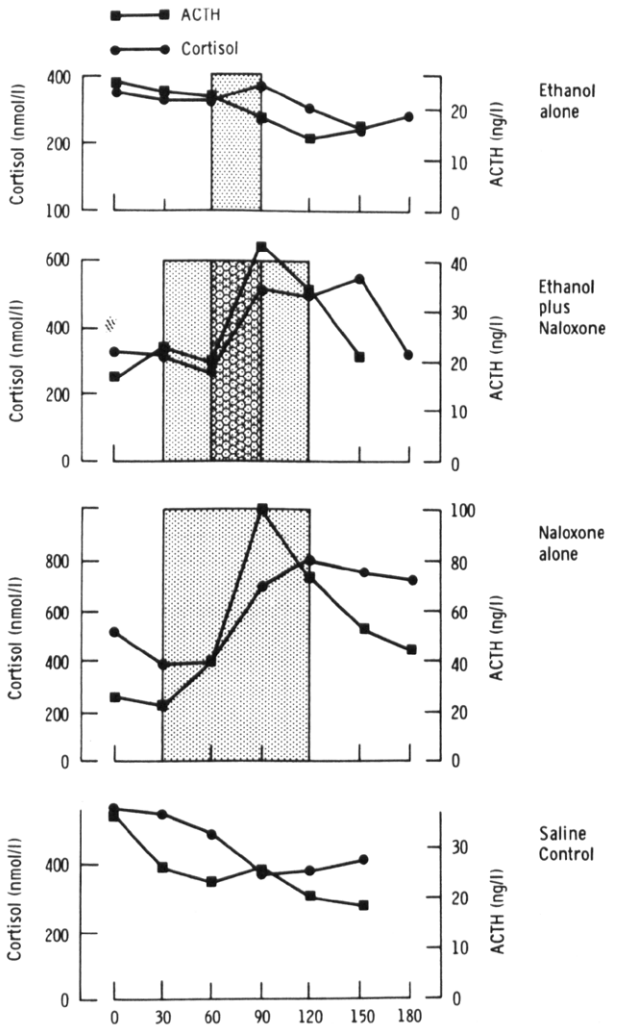

FIG. 3. Comparison of plasma cortisol (nmol/l) and ACTH (ng/l) responses in a single patient during each of four infusions: ethanol alone (1 ml/kg intravenous infusion), ethanol plus naloxone (2 mg/hr over 90 min), naloxone alone, and saline control infusions.

PRL (Figure 4)

Ethanol alone produced a variable rise in serum prolactin, but the combination of ethanol and naloxone produced a consistent rise between 60 and 90 min. Naloxone alone caused elevation in only one subject, while levels on the control day were less than 400 mU/l in all four (not illustrated).

GH (Figure 5)

While the administration of ethanol alone produced a small rise in serum GH in two subjects, levels remained low in all four when naloxone was added. When naloxone was given alone there was a small fall followed by a rise in three subjects (Fig. 6).

Alcohol and Glucose

Peak blood alcohol levels tended to be lower on the

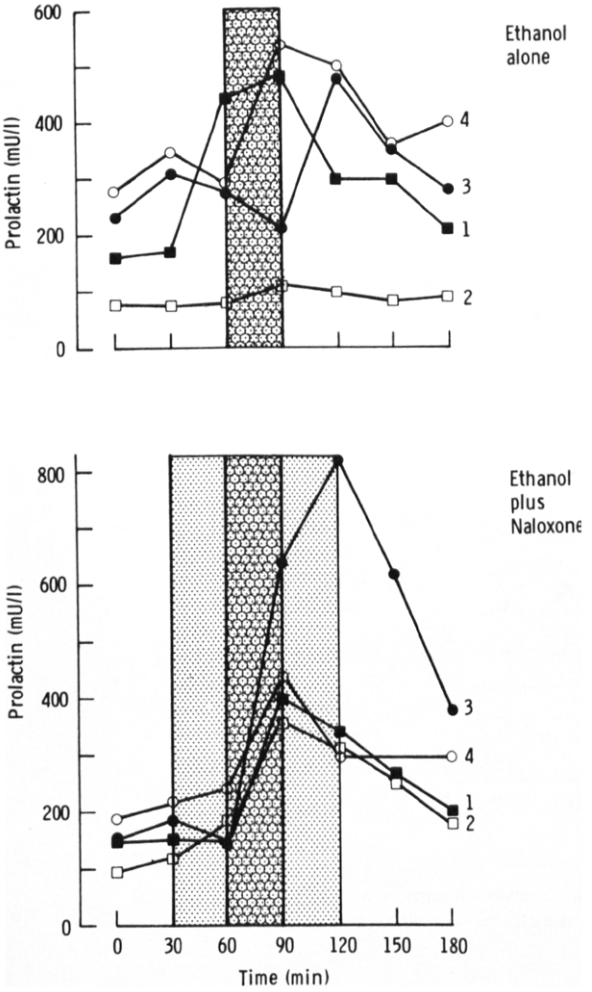

FIG. 4. Effect of ethanol infusion (1 ml/kg in 500 ml normal saline over 30 min) and of ethanol infusion with naloxone (2 mg/hr over 90 min) on serum prolactin levels.

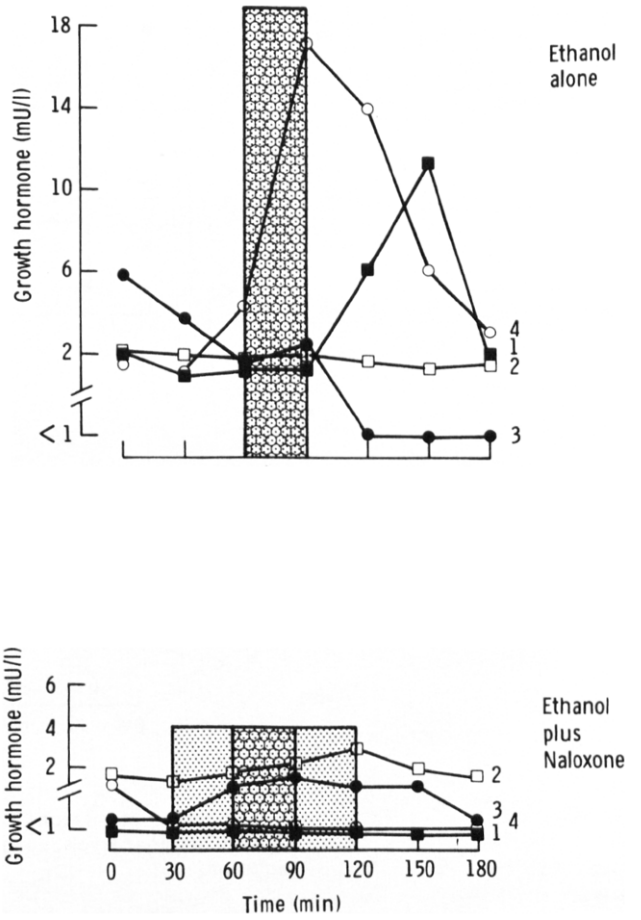

FIG. 5. Effect of ethanol infusion (1 ml/kg in 500 ml normal saline over 30 min) and of ethanol infusion with naloxone (2 mg/hr over 90 min) on growth hormone levels.

ethanol plus naloxone day (mean 25.06 mmol/1, 115.8 mg/100 ml) than on the day ethanol was given alone (mean 28.19 mmol/1, 130.3 mg/100 ml) but the difference was not significant. All blood glucose levels lay between 3.0 and 4.6 mmol/l (54 and 82 mg/100 ml).

DISCUSSION

The demonstrable endocrine changes induced by ethanol vary with the conditions of study. In this experiment we studied only the effects of acute ethanol infusion in normal female volunteers, and their modification by naloxone.

It was not possible to demonstrate an effect of ethanol alone on plasma cortisol and this finding conflicts with previous reports [4,6]. Jenkins and Connolly used a virtually identical protocol and found a consistent elevation of plasma cortisol in female subjects whose blood alcohol levels rose above 100 mg/100 ml (21.6 mmol/1). Similarly, it was not possible to confirm a previous report that naloxone alone may produce a rise in plasma cortisol [8]. However, this latter study differed from the present one in that larger doses of naloxone (10 and 20 mg) were given, by bolus injection to male subjects.

The combination of ethanol and naloxone produced a rise in plasma cortisol and ACTH in three of four subjects. The close correspondence between changes in plasma ACTH and plasma cortisol indicates that the effects of ethanol and of naloxone are, in this instance, directed at the hypothalamus and pituitary, rather than directly at the adrenal cortex.

Opiates and opioid peptides cause elevation of serum PRL and GH, although administration of the opiate antagonist, naloxone, to normal human volunteers has not been found to have any consistent effect. In the present study this lack of effect is confirmed, although a small initial fall in serum GH was noted in three of four subjects (Fig. 6). Nonetheless, the combination of naloxone and ethanol caused a prompt rise in serum PRL in all four, while serum GH levels were suppressed. The explanation for these changes is not apparent but again they suggest an interaction between ethanol and central opioid pathways.

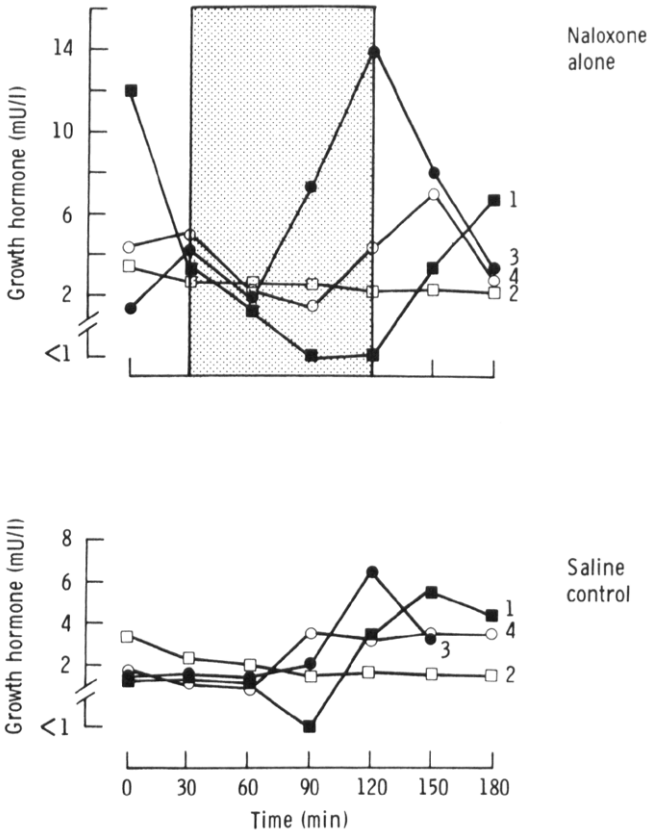

FIG. 6. Effect of naloxone infusion (2 mg/hr over 90 min) on serum growth hormone levels, compared with the effects of control saline infusion.

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