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# Hormonal Changes During Alcohol Intoxication and Withdrawal

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YLIKAHRI, R. H., M. O. HUTTUNEN AND M. HÄRKÖNEN. *Hormonal changes during alcohol intoxication and withdrawal.* PHARMAC. BIOCHEM. BEHAV. **13**: Suppl. 1, 131–137, 1980.—The endocrine effects of alcohol are briefly reviewed. Alcohol enhances glucose-induced insulin secretion and may thus cause reactive hypoglycemia. However, inappropriate insulin secretion is not the reason for alcohol-induced hypoglycemia in fasted subjects. The direct effects of alcohol on thyroid function in humans are small, although alcoholics often have low concentrations of thyroid hormones in their plasma because of liver damage. Alcohol increases cortisol secretion from adrenal cortex either by increasing ACTH secretion or, more probably, by directly stimulating the adrenals. Alcohol also increases aldosterone secretion. The production of epinephrine and norepinephrine by the adrenal medulla is increased during alcohol intoxication and withdrawal. Plasma testosterone concentration is decreased during hangover and during alcohol withdrawal. The decrease is due to direct effects of alcohol on the testes, because plasma LH concentration is increased simultaneously. Alcohol has no significant effect on the LRH-induced secretion of LH. Plasma growth hormone concentration is decreased during alcohol intoxication and increased during hangover. TRH-induced secretion of prolactin is increased during alcohol intoxication and inhibited during hangover and withdrawal. The last finding suggests that there is dopaminergic overactivity in hypothalamus during alcohol withdrawal.

Alcohol Ethanol Endocrine function Gonadal function Testosterone Luteinizing hormone Prolactin Growth hormone Intoxication Hangover Withdrawal

ALTHOUGH feminization, gynecomastia and testicular atrophy of cirrhotic alcoholics have been known for decades, the general interest in alcohol-induced hormonal changes has been small compared to the very active research into the metabolic and neural effects of alcohol. Recently, however, the development of radioimmunological techniques has made it possible to study more thoroughly and accurately the effects of alcohol on the endocrine system. These studies have shown that alcohol has marked effects on many endocrine glands and that the alcohol-induced changes in the secretion of hormones may be involved in the pathogenesis of many metabolic, behavioral and morphological disturbances caused by alcohol. The increased interest in the endocrine effects of alcohol is also reflected in the number of recent review articles in that area [1, 17, 38, 42, 51, 57, 62, 64].

The purpose of this paper is not to give an extensive, detailed review of all endocrine effects of alcohol. First, we shall briefly consider the effects of alcohol on pancreatic, thyroid and adrenal function, and then we shall discuss, in more detail, the effects of alcohol intoxication, hangover and the more severe alcohol withdrawal syndrome on pituitary and gonadal function in the light of our own studies.

## EFFECTS OF ALCOHOL ON THE ENDOCRINE FUNCTION OF PANCREAS

The alcohol-induced hypoglycemia in fasted subjects has been known for almost forty years [36] and the effects of alcohol on insulin secretion are known quite well [37]. It is evident that alcohol as such has, if any, a very small effect on basal insulin secretion [30,41], and that inappropriate insulin secretion is not the cause of alcohol-induced fasting hypoglycemia [36]. There is evidence, however, that alcohol potentiates the insulin secretion stimulated by glucose [30, 37, 39, 41]. Thus, alcohol ingested together with rapidly absorbed carbohydrates may cause an excessive insulin secretion and reactive hypoglycemia [37, 41, 44]. This phenomenon may also be of practical significance, for it has been speculated that the alcohol-induced reactive hypoglycemia could even be a contributive cause of road accidents [44].

The symptoms of hangover and also some symptoms of a more severe alcohol withdrawal syndrome resemble those caused by hypoglycemia. Consequently, hypoglycemia has been thought to play an important role in the pathogenesis of hangover [23,60]. In our own controlled studies on the pathogenesis of hangover we found somewhat lowered blood glucose levels during the hangover period, but there was no correlation between blood glucose concentration and the intensity of hangover [64,65]. In addition, hangover could not be cured by the administration of glucose or fructose which elevated the blood glucose levels [68]. Thus increased insulin secretion and low blood glucose concentration seem not to be of importance in the pathogenesis of hangover.

There is very little information about the effects of ethanol on the secretion of pancreatic hormones other than insulin. It is known that alcohol increases the secretion of glucagon in at least man [45], pig [52] and rat [26]. The physiological significance of this alcohol-induced glucagon secretion is obscure, but it may contribute to the depletion of hepatic glycogen stores during alcohol intoxication. It may also play a role in the pathogenesis of ketoacidosis sometimes found in alcoholics. There are no data about the effect of alcohol on the secretion of other pancreatic hormones such as somatostatin and pancreatic polypeptide.

### EFFECTS OF ALCOHOL ON THYROID FUNCTION

Thyroid hormones have been shown to alter the voluntary alcohol consumption of animals [22] and to modify the metabolism [21,69] and metabolic effects [32,63] of alcohol, but it is not known whether these findings have any implications in humans.

Chronic alcohol ingestion has been found to increase the oxygen consumption of the rat liver in a similar manner to thyroxine ($T_4$) [25,61]. However, it is not known whether this change is really mediated by thyroid hormones. It has been shown that alcohol does not increase the concentrations of ($T_3$) in rat plasma.

The results of human studies on the effects of alcohol on thyroid function have been somewhat conflicting. Goldberg reported that hypothyroidism is more frequent in alcoholics than in the nonalcoholic population [19,20]. This finding, however, has not been confirmed in later studies [49]. In an extensive study on 40 chronic alcoholics, Van Thiel *et al.* [59] found significantly decreased plasma $T_4$ and $T_3$ levels in alcoholics compared to controls of the same age. Plasma concentration of thyroid stimulating hormone (TSH) was slightly increased in these alcoholics. All these patients, however, had some kind of liver damage and it is possible that the changes found in the thyroid function of the alcoholics are not directly caused by alcohol but are secondary to the liver damage, which is known to affect the metabolism of the thyroid hormones. In acute experiments alcohol seems to have no significant effect on the plasma concentrations of the thyroid hormones or on the secretion of TSH [59,66], and the direct effects of alcohol on human thyroid function are probably small.

### EFFECTS OF ALCOHOL ON ADRENAL GLAND

Although alcohol is often drunk to relieve stress, the endocrine reaction of the body to alcohol is largely similar to the general stress reaction. Very early studies showed that alcohol decreased the content of ascorbic acid and cholesterol in the adrenal cortex of experimental animals [see 62]. This was regarded as an indication of an increased synthesis of cortisol and other steroids. Later, numerous studies have shown that alcohol actually increases the concentration of cortisol in plasma [5, 42, 62] and the excretion of its metabolites into the urine. In our own studies with healthy male and female volunteers we found significantly increased plasma cortisol concentrations during both alcohol intoxication and hangover [66].

Some previous studies gave indirect evidence that increased cortisol production was mediated through increased secretion of adrenocorticotropic hormone (ACTH) from the pituitary (see [42,62]). However, recent studies, in which plasma ACTH concentrations have been measured directly by radioimmunoassays, suggest that alcohol has no acute effects on plasma ACTH levels. Leppäluoto *et al.* [31] studied the effect of alcohol on pituitary function in healthy male volunteers and found no changes in plasma ACTH concentrations during a period of 15 hours after the ingestion of alcohol. In a briefer experiment (4 hours) Jeffcoate *et al.* [27] also found that alcohol had no effect on the plasma concentrations of ACTH or β-lipotropin, which is usually secreted together with ACTH. On the other hand, there is evidence that alcohol may directly stimulate the adrenal cortex to produce cortisol [13]. Thus the question about the pathogenesis of the alcohol-induced hypercortisolemia is still open.

Chronic heavy drinking of alcohol may cause permanently elevated plasma cortisol levels and may lead to a disease resembling Cushing's syndrome caused by pituitary adenoma secreting ACTH. Several so called pseudo-Cushing's syndromes in alcoholics have been reported recently [18, 47, 50]. Clinically and biochemically these patients are very similar to those having "real" Cushing's syndrome but the symptoms and signs are usually reversible after cessation of drinking. It is not known whether the pseudo-Cushing's syndrome is caused by increased ACTH secretion or by direct stimulation of the adrenal cortex by alcohol [13]; nor are there data available about the incidence of pseudo-Cushing's syndrome, but it is probably more common than assumed.

Alcohol has also been shown to stimulate the secretion of weakly androgenic steroids, such as androstendione and dihydroepiandrosterone, from the adrenal cortex. These steroids can be converted to estrone in peripheral tissues and may so contribute to the feminization of alcoholics [57].

Several studies have shown that alcohol increases the excretion of epinephrine and norepinephrine and their metabolites into the urine [43,46]. The concentrations of these amines in plasma are also most probably elevated, but as far as we know there are no controlled studies in which these concentrations have been adequately measured. In animal experiments increased activities of the enzymes involved in the synthesis of catecholamines in adrenal medulla have been reported during alcohol intoxication and withdrawal [14]. In the same study an increased turnover of epinephrine and norepinephrine in adrenal medulla was found after the ingestion of alcohol. Accordingly, alcohol most probably increases the production and secretion of catecholamines in adrenal medulla.

Part of the symptoms of alcohol intoxication, hangover and withdrawal such as tachycardia, rise in blood pressure, palpitation, tremor and sweating, greatly resemble those of sympathetic overactivity. Moreover, many of these symptoms can be blocked by α- and β-adrenergic blocking agents, and so increased secretion of catecholamines may play a role in the pathogenesis of hangover and the alcohol withdrawal syndrome. Catecholamines may also contribute to alcohol-induced hypertension.

### EFFECTS OF ALCOHOL ON HORMONES REGULATING WATER AND ELECTROLYTE METABOLISM

Alcohol-induced diuresis has long been known, and many experiments have shown that alcohol increases water excretion as long as its concentration in blood is increasing (see [4]). When blood alcohol concentrations begins to decrease the diuresis is diminished [4, 34, 35]. There is indirect evidence that the alcohol-induced diuresis could be due to the inhibition of the secretion of antidiuretic hormone (Arginine vasopressin = AVP) from the pituitary [28,48]. However, in

a recent study with human volunteers Linkola *et al.* found no decrease in the plasma concentration of immunoreactive AVP during acute alcohol intoxication [35], although excretion of urine was significantly increased. This finding is not in agreement with the earlier studies and suggests that alcohol may increase water diuresis by mechanisms other than the inhibition of AVP secretion. It should be remembered, however, that AVP is only weakly antigenic and its radioimmunological measurement is not very easy, which makes it difficult to measure small concentrations accurately. In the study of Linkola *et al.* [35] diuresis was significantly decreased during hangover and simultaneously the AVP concentration was clearly elevated, which agrees well with the earlier findings.

Plasma concentrations of sodium and potassium are largely regulated by the renin-angiotensin-aldosterone system. The effects of ethanol on this system have been little studied. Linkola *et al.* reported that plasma renin activity was increased both during alcohol intoxication and hangover compared to the values measured before drinking [33]. Plasma aldosterone concentration was decreased during intoxication but significantly elevated during hangover. In this particular study, however, no adequate control experiments were done, and the changes found in plasma renin activity and aldosterone concentration may be caused more by water restriction than by alcohol itself. In a later study in which the experimental design was such that the artefactual effect of water intake and restriction could be eliminated, the ethanol-induced changes in plasma renin activity and aldosterone concentration were much smaller than in the previous experiment [34]. Nevertheless, the results do suggest that ethanol may have effects on the renin-angiotensin-aldosterone system and so alter the electrolyte balance of the body. These alterations could be a mechanism by which alcohol causes hypertension.

### EFFECTS OF ALCOHOL ON GONADAL FUNCTION

The impairment of gonadal function in cirrhotic alcoholics has been known for a long time, although the pathogenesis of the phenomenon is not fully clear. Is it due to liver cirrhosis or caused by alcohol itself? Recent studies on the acute and chronic effects of alcohol on the gonads of animals and human volunteers as well as the evaluation of gonadal function in alcoholics have shed much light on the question. In this section we shall consider mainly the effects of alcohol intoxication and withdrawal on gonadal function.

In animal experiments (both acute and chronic) alcohol treatment has been found to decrease plasma testosterone concentration [2, 3, 7, 10, 11, 53]. There seem to be several mechanisms for this phenomenon. In rats alcohol has been found to decrease the concentration of luteinizing hormone (LH) in plasma [6, 7, 10, 11]. This is probably due to inhibition of the secretion of the releasing hormone (LRH) from the hypothalamus [6,11]. The inhibition of LRH secretion may in turn be attributable to alcohol-induced changes in the metabolism of hypothalamic biogenic amines, which are known to regulate the secretion of the releasing hormones. On the other hand, alcohol treatment causes histological changes in the testes of the rats and may so inhibit testosterone production also at the testicular level [2, 12, 40, 53, 55]. The mechanism of the toxic effect of alcohol on the testes is unknown, but it may disturb the metabolism of vitamin A which is known to regulate testosterone production of the testes. Alcohol can induce a change of the testicular redox state and so inhibit the conversion of vitamin A (retinol) to its active form retinal [54]. In addition, acetaldehyde effectively inhibits the production of testosterone [8,9]. Anyway, alcohol seems to affect the gonadal function of rats both at the hypothalamic-pituitary and at the gonadal level.

Alcohol has also been found to markedly decrease plasma testosterone concentration in humans [40, 53, 67]. In our own studies with human volunteers receiving alcohol (1.5 g/kg body wt.), we found a significant decrease in plasma testosterone concentration during the hangover period 12–20 hours after the ingestion of alcohol [67]. The concentration of LH in plasma was simultaneously increased, suggesting that the decrease in testosterone concentration was mainly a result of the direct effect of alcohol on the testes.

Because in experiments with human volunteers the plasma testosterone concentrations were lowest in those subjects who had the most severe hangover, we studied plasma testosterone levels in alcoholics who were admitted to the hospital to interrupt their drinking period and who had severe withdrawal symptoms [24]. None of the alcoholics had any biochemical signs of severe liver disease in spite of relatively long drinking histories. Their testosterone concentrations were within normal limits during the most severe withdrawal symptoms, but they increased significantly when the withdrawal symptoms diminished, the plasma LH levels were simultaneously decreased. This finding too suggests that in man the primary acute effect of alcohol on the testosterone production may be at the testicular level. However, in this and in hangover studies, unspecific stress may have played a role in the decrease of plasma testosterone production, because low testosterone concentrations have been reported after other kinds of physical [15] and psychological [29] stress.

Van Thiel has found that alcohol decreases the LRH-induced release of LH in man [53]. We studied the effects of acute alcohol intoxication and subsequent hangover on LRH-induced LH release both in healthy males [66] and females. The males received an alcohol dose of 1.5 g/kg body wt., and females 1.2 g/kg body wt. over the first three hours of the experiment. LRH (100 $\mu$g) was injected intravenously during maximal intoxication, 4 hours after the start of drinking, and again during most intense hangover, 10 hours later. Each subject served as his/her own control by participating in a second identical experimental session during which water was given instead of alcohol. Because of the great variation in the LH secretion of females according to the menstrual cycle, all the experiments in females were performed on day 21 of the cycle.

No effect of alcohol on basal or LRH-stimulated levels of LH were found in men [66]. The responses of LH to LRH were of about the same magnitude during alcohol intoxication and hangover.

In females the individual variations in plasma LH concentrations were greater than in males (Fig. 1). Alcohol had no significant effect on the basal plasma LH levels. During alcohol intoxication the response of LH to LRH was about the same as during the control period but during hangover the response was somewhat exaggerated (Fig. 1).

We also studied LRH-induced LH secretion during the withdrawal symptoms of 8 chronic alcoholics who were hospitalized to interrupt their drinking period. The age of the alcoholics ranged from 25 to 50 years. None of them had any physical or biochemical signs of severe liver damage. The first LRH test was performed one day after the admission when the withdrawal symptoms were most severe. The re-

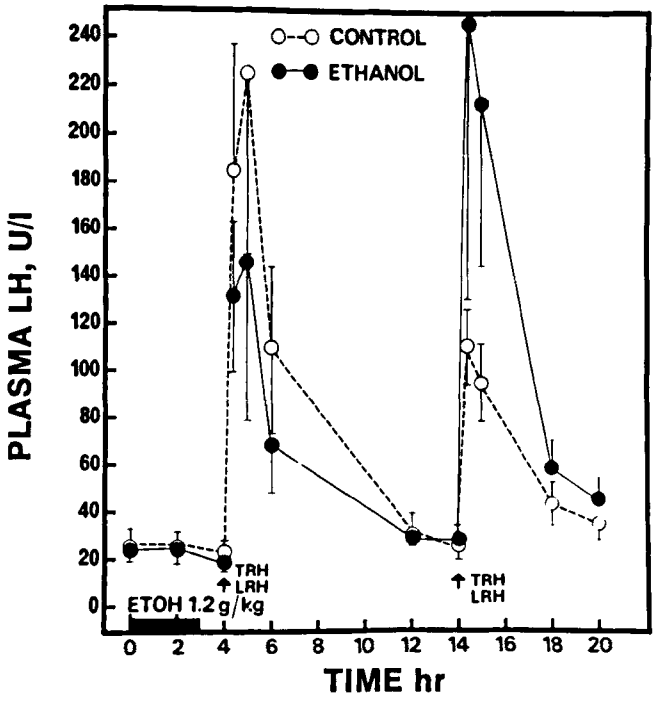


FIG. 1. Effect of alcohol on the secretion of luteinizing hormone (LH) induced by the releasing hormone (LRH) in healthy females. Alcohol (1.2 g/kg body wt.) was given orally as 15% (w/v) solution during first 3 hours of the experiment after fasting 6 hours. All experiments were started at 6 p.m. LRH (100 $\mu$g) was injected intravenously 4 and 14 hours after the start of the experiment. Experimental subjects were in recumbent position throughout and blood samples were collected through a plastic cannula. All experiments were performed on the 21st day of the menstrual cycle. Each subject served as her own control by participating in second identical experimental session during which she received water instead of alcohol. Results are means ± SE of the values from 7 women.

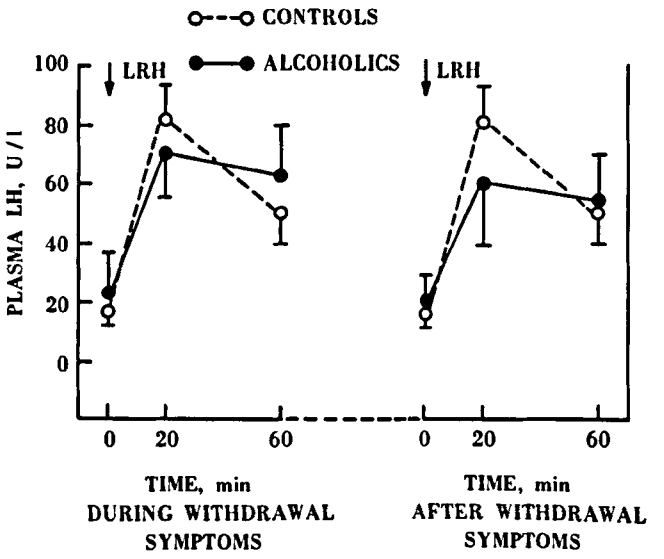


FIG. 2. Effect of LRH on the secretion of LH in alcoholics during and after withdrawal syndrome. Eight alcoholics with recent drinking periods of 3 to 12 weeks were admitted to the hospital to interrupt their drinking. Each had severe withdrawal symptoms. LRH (100 $\mu$g) was injected intravenously 16–20 hours after the admission and 10 days later. All the LRH tests were performed at 8 a.m. Blood samples were collected through a plastic cannula. The control group consisted of 16 healthy men of the same age. Results are means ± SE.

sponse of LH to LRH was normal (Fig. 2). The LRH test was repeated 10 days later when the patients no longer had withdrawal symptoms. The response was again normal (Fig. 2).

On the basis of the above results we can conclude that plasma testosterone concentrations are decreased in man during hangover and perhaps also during a more severe alcohol withdrawal syndrome. The basal concentrations of LH are somewhat increased simultaneously but alcohol does not have significant effects on the LRH-induced LH release. Thus the acute testosterone lowering effect of alcohol in man seems to be mainly due to direct effects on the testes, although in chronic alcoholics also the pituitary function is affected [56, 57, 58].

### EFFECTS OF ALCOHOL ON THE SECRETION OF GROWTH HORMONE AND PROLACTIN

It has been reported previously that alcohol inhibits the secretion of growth hormone (GH) during sleep [31]. In our own studies we investigated the effects of acute alcohol intoxication and hangover on the secretion of GH in healthy male and female volunteers (same experiments in which LH and prolactin secretion were studied). In male volunteers we found no consistent effect of alcohol on GH secretion [66]. In

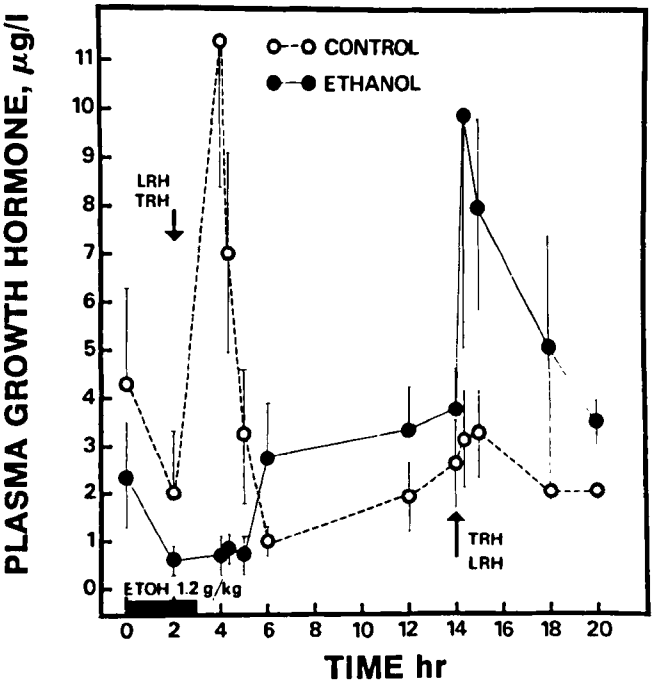


FIG. 3. Effect of alcohol on the secretion of growth hormone (GH) in healthy females. Volunteers and experimental design as described in FIG. 1. Results are means ± SE.

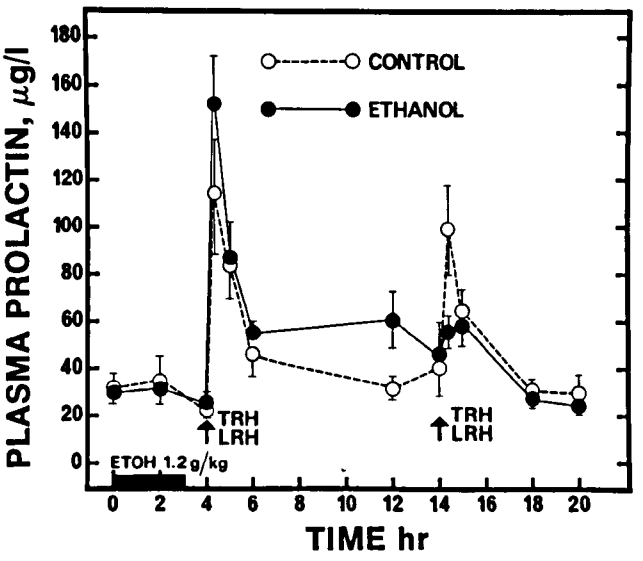


FIG. 4. Effect of alcohol on the secretion of prolactin (PRL) induced by thyrotropin releasing hormone (TRH) in 7 healthy women. Volunteers and experimental design as in FIG. 1. TRH (200 μg) was injected intravenously together with LRH. Results are means ± SE.

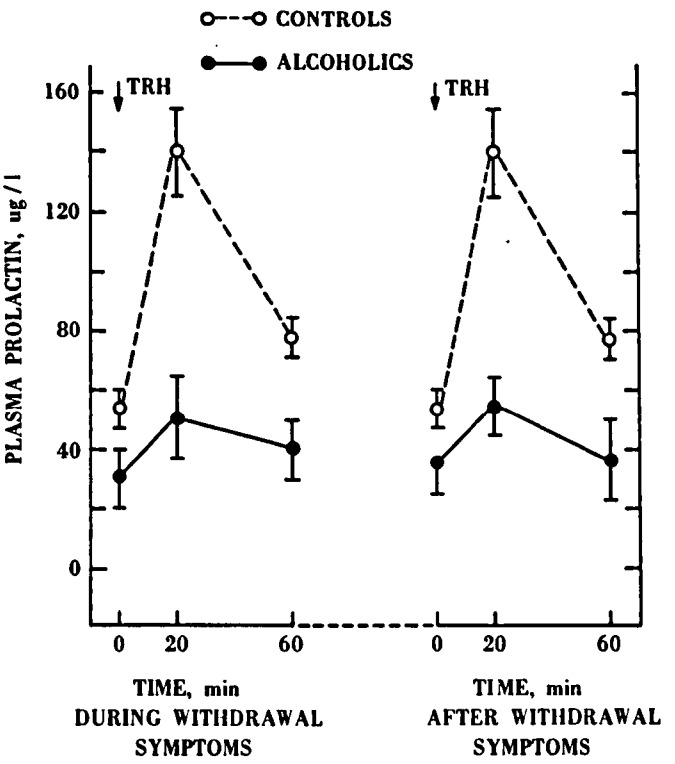


FIG. 5. Effect of TRH on the secretion of PRL in 8 alcoholics during and after withdrawal syndrome. Patients and experimental design as in FIG. 2. TRH (200 μg) was injected intravenously together with LRH. Results are means ± SE.

these experiments, however, the volunteers were free to walk around and thus their physical activity varied considerably. It is known that physical activity affects GH secretion, which is perhaps why there have been large individual variations of plasma GH levels in male volunteers.

In experiments on healthy female volunteers the subjects were in a recumbent position all the time, and the individual variations were much smaller than in experiments on males. In females we found a significant decrease in GH secretion during alcohol intoxication. However, during hangover the GH concentration was significantly higher than during the control period (Fig. 3). In alcoholics the GH concentrations were within normal limits both during acute intoxication and withdrawal (Ylikahri and Huttunen, unpublished).

Plasma prolactin (PRL) concentrations are often increased in chronic alcoholics, especially in those who have gynaecomastia [56], but the acute effects on plasma PRL concentrations have been found to be small [16,66]. In our own studies with healthy male volunteers we found no acute effect of alcohol on basal plasma PRL concentration [66]. The response of PRL to the injection of TRH was, however, exaggerated during alcohol intoxication, and totally blocked during subsequent hangover [66]. In similar experiments with female volunteers the results were exactly the same: the basal PRL concentrations were not affected by alcohol, the response of PRL to TRH was exaggerated during alcohol intoxication, and totally blocked during hangover (Fig. 4). In the studies of male alcoholics with withdrawal symptoms (same patients in whom the effect of LRH on LH secretion was studied), the response of PRL to TRH was inhibited during withdrawal compared to normal controls (Fig. 5). The patients were again studied 10 days later, but even then the TRH-induced PRL secretion was inhibited as much as during withdrawal (Fig. 5). Unfortunately, we could not study the patients later. In more recent studies on alcoholics without withdrawal symptoms we have found normal or even exaggerated responses of PRL to TRH (Ylikahri and Välimäki, to be published).

We do not know what is the physiological significance of the above mentioned changes in the secretion of PRL and GH during hangover and withdrawal, but some speculations can be presented. It is known that dopamine is the main regulator of the PRL secretion, inhibiting it effectively. On the other hand, dopamine is known to stimulate GH secretion in healthy subjects. Thus the decreased response of PRL to TRH during hangover and withdrawal syndrome may indicate increased dopaminergic activity in the hypothalamus under these conditions. The increased GH secretion in female volunteers during hangover gives additional support for the hypothesis. Nevertheless, the hypothesis is still very speculative and it must be tested in animal experiments in which plasma hormone concentrations and hypothalmic amines can be measured simultaneously. We do, however, believe that results of this kind show that neuroendocrine studies may elucidate the mechanisms of the actions of alcohol on the central nervous system in humans as well.

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