Tubero-infundibular dopaminergic function in cirrhotic patients: evaluation by nomifensine and domperidone

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Abstract. Cirrhotic patients reportedly show alterations of anterior pituitary hormone secretion, which may reflect an underlying defective central neurotransmitter function. In this study, we have investigated the catecholaminergic control of prolactin (Prl) and growth hormone (GH) secretion in cirrhotic patients by means of an indirectly acting dopamine (DA) and norepinephrine agonist, nomifensine (Nom), and a DA receptor antagonist, domperidone (Dom).

Basal GH levels were higher in the 12 female and male cirrhotic patients than in the 12 age- and sex-matched normal controls, while no difference was present in basal Prl values.

Administration of Nom (200 mg po) suppressed basal Prl levels (at least 30% inhibition at three consecutive times post-drug administration) in 6/12 controls and in 6/12 cirrhotic patients, the frequency of negative responses not being different between the two groups. Nom induced a slight elevation of GH levels in controls, and evoked a more marked and sustained GH increase in cirrhotic patients.

Administration of Dom (4 mg iv) induced similar Prl increments in 6 male controls and 6 male cirrhotic patients.

Normal Prl responsiveness to Nom and Dom points to the existence of preserved tubero-infundibular DA function and modulation of pituitary DA receptors in the cirrhotic patients investigated. Higher GH responsiveness to Nom is compatible with a different bioavailability of the drug.

The presence of hypothalamo-hypophyseal changes in patients affected by severe liver disease is strongly suggested by the derangement of anterior pituitary (AP) hormone secretion. High basal levels of growth hormone (GH) and prolactin (Prl) and an inappropriate secretion of gonadotrophins have been reported by many investigators in cirrhotic patients (Cameron et al. 1972; Van Thiel et al. 1975, 1976). In addition, most of them exhibit an anomalous GH response to administration of thyrotrophin-releasing hormone (TRH) and a paradoxical plasma GH rise after glucose loading (Panerai et al. 1977; Becker et al. 1969). These abnormalities of AP hormone secretion may be due to defective function of central neurotransmitters including dopamine (DA), a deficiency of which has been postulated on the basis of biochemical studies in rodents and humans (James et al. 1976; Baldessarini & Fisher 1977).

In this respect the presence of an impaired dopaminergic tone in the hypothalamus of cirrhotic patients has been suggested based on the reduced ability of L-dopa and L-dopa plus carbidopa – a peripheral L-aromatic amino acid decarboxylase inhibitor – to depress basal Prl levels, or to induce a significant GH rise (Borzio et al. 1981).

In the present study, we decided to investigate the function of the hypothalamic dopaminergic system by evaluating Prl secretion in cirrhotic patients, after administration of the indirect DA agonist nomifensine (Nom) and the DA receptor blocker domperidone (Dom), two drugs whose
The effect on Prl secretion is dependent upon the functional integrity of the tubero-infundibular dopaminergic (TIDA) system (Müller et al. 1981). In addition, we evaluated in the same patients the responsiveness of GH secretion to the same agents.

Materials and Methods
The present study was carried out in 12 patients, 7 men and 5 women, aged 30–61 years, with alcoholic cirrhosis of the liver, whose clinical and laboratory characteristics are reported in Table 1. No patient was obese or gave a family history of diabetes mellitus; clinical signs of hyperoestrogenism were present in some of the males; 4 females were post-menopausal, one was in the early follicular phase (no. 5). In the pre-admission period, none was taking any medication known to affect hormone secretion (e.g. metoclopramide, cimetidine, spironolactone or neuroactive drugs). None of the age- and sex-matched controls who underwent the same experiments had abnormal liver function tests or was taking any drug.

All subjects were given a standard dose of Nom (Psicronizer, Hoechst A.G., 200 mg po) or Dom (Motilium, Janssen, 4 mg iv), a period of two days separating each drug test in the same subject. The experiments were always performed between 08.30 and 09.00 h after an overnight fast; an indwelling catheter was inserted into a forearm vein 30 min before the experiment and kept open by a slow infusion of normal saline solution. After two baseline blood samples were taken, 30 min and immediately before testing, Nom or Dom were administered and further samples were obtained 30, 60, 90, 120, 180, 210, 240 and 300 min later.

Plasma was obtained by centrifugation and frozen at −20°C until assayed. After Nom administration plasma Prl was evaluated in 12 cirrhotic patients and 12 controls, plasma GH in 10 cirrhotic patients and 10 controls; after Dom injection, plasma Prl was evaluated in 6 cirrhotic patients and 6 controls, plasma GH in 8 cirrhotic patients and 8 controls. In addition, oestradiol-17β (E2) and testosterone (T) were evaluated in baseline blood samples of 11 patients.

GH, Prl and T assays were done using reagents supplied by BIODATA (Milan, Italy): the sensitivity of the assays was 0.5 ng/ml (WHO 66/217), 0.3 ng/ml (WHO 71/222) and 6 ng/dl, respectively. The E2 assay was done by the kit supplied by SORIN CEA-IRE (Saluggia, Italy), which has a sensitivity of 35 pg/ml.

Values, expressed in ng/ml (GH and Prl), ng/dl (T and E2), were evaluated statistically according to Student's t-test for unpaired data.

Table 1. Clinical and laboratory characteristics of the patients with alcoholic liver cirrhosis1.

<table>
<thead>
<tr>
<th>Patients</th>
<th>Age years</th>
<th>SGOT U/l</th>
<th>Total bilirubin mg/dl</th>
<th>Serum albumin g/dl</th>
<th>γ GT U/l</th>
<th>Serum ammonaemia μg/dl</th>
<th>Preceding encephalopathy</th>
<th>T ng/dl</th>
<th>E2 ng/dl</th>
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<tr>
<td>1 Male</td>
<td>57</td>
<td>16</td>
<td>3.90</td>
<td>2.40</td>
<td>39</td>
<td>88</td>
<td>yes</td>
<td>420</td>
<td>6.8</td>
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<tr>
<td>2 Male</td>
<td>55</td>
<td>20</td>
<td>3.80</td>
<td>3.40</td>
<td>16</td>
<td>158</td>
<td>yes</td>
<td>462</td>
<td>9.3</td>
</tr>
<tr>
<td>3 Female</td>
<td>51</td>
<td>52</td>
<td>2.25</td>
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<td>540</td>
<td>94</td>
<td>yes</td>
<td>75</td>
<td>3.8</td>
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<tr>
<td>4 Female</td>
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<td>30</td>
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<td>74</td>
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<tr>
<td>5 Female</td>
<td>30</td>
<td>100</td>
<td>0.65</td>
<td>4.12</td>
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<td>75</td>
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<td>2.10</td>
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<td>65</td>
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<tr>
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<td>97</td>
<td>–</td>
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<tr>
<td>10 Male</td>
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<td>58</td>
<td>59</td>
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<tr>
<td>11 Male</td>
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<tr>
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<td>61</td>
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<td>41</td>
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</table>

Normal values 2–20 < 1 3.8–5.2 4–28 18–48 Male: 350–900 1.0–4.0 Female: 40–150 4.5–15 0–1

1 Ascertained by biopsy.
Results

Basal plasma GH levels were significantly higher in cirrhotic than in control subjects (3.0 ± 0.7 ng/ml vs 0.7 ± 0.1 ng/ml, respectively, \( P < 0.02 \)), whilst no significant difference was present between the two groups as far as Prl levels are concerned (8.2 ± 0.8 ng/ml vs 7.7 ± 1.2 ng/ml, respectively, \( P = \text{NS} \)).

Fig. 2 shows the responsiveness of cirrhotic patients and controls to administration of Nom. Only basal and nadir values (mean of the three lowest consecutive post-drug Prl levels) are depicted. Nom suppressed basal Prl levels (at least 30% inhibition) in 6 out of 12 controls and in 6 out of 12 cirrhotic patients, the frequency of negative responses being not significantly different between the two groups.

Three out of 6 non-responder cirrhotic patients were post-menopausal females (nos 4, 6, 9).

Administration of Nom induced a slight elevation of GH levels in the controls (from 0.7 ± 0.1 ng/ml to peak levels of 7.5 ± 2.1 ng/ml at 90 min), but evoked a more marked and sustained GH increase in cirrhotic patients (from 2.9 ± 0.5 ng/ml to peak levels of 8.6 ± 1.8 ng/ml at 210 min).

Fig. 1.

Individual Prl responses to nomifensine (Nom, 200 mg po) in cirrhotic patients (left panel) and controls (right panel). Prl values are expressed as S/B (ratio between the mean of three consecutive lowest post-drug Prl values (S) and the basal levels (B)).
levels. Effect present A elicited levels: (Fig. 3. levels were from and patients: Nomifensine, 0.40. levels demonstrated (Casanueva et al. 1982). Similarly, Nom does not inhibit Prl secretion in subjects with a prolactinoma (Genazzani et al. 1980).

Domperidone, a DA receptor blocker, which does not cross the blood brain barrier (Laduron & Leysen 1979), stimulates Prl secretion by inhibiting the action of DA released from TIDA neurons on pituitary lactotrophs. Therefore, Dom fails to affect Prl secretion in conditions of impaired central dopaminergic function (Casanueva et al. 1982), or to induce Prl release from rat pituitaries located under the kidney capsule (unpublished results) and, like Nom, does not increase Prl levels in patients with a prolactinoma (Camanni et al. 1980). Nom induces a consistent inhibition of Prl levels in normal women when the basal values of the hormone are sufficiently high (> 12 ng/ml) but has little effect on Prl levels in normal women with very low baseline Prl values, or in men (Genazzani et al. 1980).

In view of these findings the inability of Nom to decrease Prl secretion in some cirrhotic patients does not necessarily indicate defective hypothalamic dopaminergic function. In fact, the drug was also inactive in this respect in 6 controls, and, moreover, it has been shown by us that normal women are hyporesponsive to Nom with advancing age (Locatelli et al. 1982); interestingly, 3 of the Nom non-responder patients were post-menopausal women.

In support of this proposition Dom was able to increase Prl levels to a similar extent in the cirrhotic and control subjects, which should denote the intact TIDA neuronal function.

Further evidence favouring preserved TIDA neuronal function was that all our patients had basal Prl levels no higher than the controls. At variance with other groups (Tarquini et al. 1977; Van Thiel et al. 1978) who reported increased Prl secretion in some cirrhotic patients, coupled to unresponsiveness to TRH, we also found normal Prl levels in most patients in our previous series (80 cirrhotic patients) (Salerno et al. 1979). Only 3 patients in the preceding study (Salerno et al.

![Figure 3](image-url)

Effect of domperidone (Dom, 4 mg iv) on plasma Prl levels in 6 male cirrhotic patients (□—□) and 6 controls (○—○).

A significant difference between the two curves was present at time 180, 210, 240 min (P < 0.05) (Fig. 2).

Administration of Dom increased plasma Prl levels significantly in 6 male controls (peak Prl levels: 63.5 ± 6.8 ng/ml at 30 min). The drug elicited a similar Prl rise in 6 male cirrhotic patients, though in this case peak plasma Prl values were present at 60 min (59.2 ± 12.1 ng/ml) (Fig. 3).

Dom induced only erratic changes in basal GH levels in control subjects (6 males and 2 females), whereas it induced varying GH responses in 8 patients: inhibition in 2 patients, stimulation in 3, and no change in the 3 remaining (data not shown).

Discussion

Nomifensine, an indirect DA agonist drug, inhibits Prl secretion by releasing the neurotransmitter from neuronal stores (Braestrup & Scheel-Krüger 1976; Algeri et al. 1982), but has no effect on post-synaptic DA receptors (Cocchi et al. 1979). Hence, the Prl-inhibiting action of Nom depends on the presence of sufficient intraneuronal dopaminergic stores. The drug, which inhibits Prl secretion in the intact rat, does not lower Prl secretion from a pituitary, grafted under the kidney capsule (i.e. separated from the hypothalamus) (Cocchi et al. 1979), and in rats bearing an oestrogen-induced Prl-secreting adenoma, in which a diminished function of TIDA neurons has been demonstrated (Casanueva et al. 1982). Similarly, Nom does not inhibit Prl secretion in subjects with a prolactinoma (Genazzani et al. 1980).
1979), had very high basal Prl levels and were not responsive to TRH. Unfortunately, since no dynamic testing of Prl secretion was performed with either Nom or Dom in those patients, the possibility of defective TIDA neuronal function could not be excluded in those patients.

Therefore, unlike Borzio et al. (1981), who reported a subnormal suppression of plasma Prl in cirrhotic patients after l-dopa alone, or in combination with carbidopa, a peripheral decarboxylase inhibitor (Bartholini & Pletscher 1975), and hence, activator of TIDA function, our data do not support the existence of defective dopaminergic control of Prl secretion in cirrhotic patients.

Nom induced a slight elevation of GH levels in controls, but a more clear-cut and sustained GH rise in cirrhotic patients.

Among many others, two hypotheses which may account for this result are here considered: 1) a greater sensitivity of cirrhotic patients to a catecholaminergic stimulus, since Nom is also an effective activator of norepinephrine (NE) transmission (Innes & Nicherson 1975), and NE stimulates GH release in man (Müller 1979); 2) differing pharmacokinetics of the drug in cirrhotic patients.

The first hypothesis seems unlikely since l-dopa, which also activates catecholaminergic neurons, has been reported to induce similar increases in patients and controls (Müller et al. 1979) or to be ineffective in cirrhotic patients (Borzio et al. 1981). However, no data are available on the effect of more specific noradrenergic agonists on GH secretion in cirrhotic patients.

No specific studies have been conducted on the effects of abnormal liver parenchymal function on the disappearance rate of Nom. However, it is known that in man 60–70% of ingested Nom circulates in blood bound to serum proteins (Brodgen et al. 1979). Hence, the low levels of circulating albumin present in cirrhotic patients might decrease the amount of 'bound' Nom in plasma. Since only the 'free' drug is capable to cross the brain blood barrier (BBB) and hence, to activate hypothalamic catecholaminergic neurons, this would result in a greater availability of Nom in the central nervous system of cirrhotic patients where nerve structures for GH control are located (Müller 1979). Unlike that on GH, the action of Nom on Prl is mainly exerted on (TIDA) nerve terminals of the median eminence (Apud et al. 1980), where the BBB is lacking, and would not be impaired by a different bioavailability of the drug.

Supporting this view, is the fact that the time course of the Prl inhibition by Nom in responder subjects was the same for cirrhotic patients and for controls.

In conclusion, normal Prl responsiveness to Nom and Dom would suggest the existence of preserved TIDA neuronal function, at least in the group of cirrhotic patients investigated in this study.

In contrast to Prl, GH responsiveness to Nom was greatly enhanced in cirrhotic patients, a fact which might be due to a different bioavailability of the drug or to hyperfunction of the hypothalamic noradrenergic system.

References


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