Depressed antithrombin III biological activity in opiate addicts

ANTONIO CERIELLO, PATRIZIA DELLO RUSSO, FRANCESCO CURCIO, ANGELO TIRELLI, DARIO GIUGLIANO

From the Istituto di Patologia Speciale Medica, I Facoltà di Medicina — Università di Napoli, Naples, Italy.

SUMMARY Antithrombin III activity was significantly decreased in opiate addicts, but no difference was found between addict and control groups in antithrombin III plasma concentration. Moreover, glycosylated haemoglobin concentration was increased in opiate addicts, but no correlation between glycosylated haemoglobin and antithrombin III activity was found.

These data show that in opiate addicts there is depressed biological activity of antithrombin III. Further characterisation of the molecular changes in antithrombin III in addicts is needed to establish whether the impaired activity is affected by altered glucose metabolism.

Decreased antithrombin III activity,¹ correlated with altered glucose metabolism, has been reported in diabetes; this decreased activity occurs in the presence of normal concentrations of proteins. Impaired glucose tolerance in opiate addicts has been shown by low values of glucose utilisation² and by increased concentrations of glycosylated haemoglobin³ and glycosylated proteins.⁴ We have therefore measured the concentration as well as the biological activity of antithrombin III in opiate addicts and have correlated the results with glycosylated haemoglobin values, which closely reflect glucose tolerance.⁵

Material and methods

Nineteen male addicts, who were taking heroin by intravenous injection and were attending our unit regularly for treatment, were studied. All were volunteers, aged 18–27 years, with normal body weights (58–68 kg), and with no family history of diabetes. The total heroin intake in 24 h ranged between 20 and 200 mg.

Twenty healthy men, matched for age (18–28 years) and weight (56–69 kg), acted as controls.

Citrated venous blood was obtained from a forearm vein, without stasis, after 12 h fasting. Plasma glucose concentration was measured by the glucose oxidase method. Glycosylated haemoglobin was determined with the rapid chromatographic method of Welch and Boucher.⁶

Antithrombin III activity was evaluated as heparin cofactor activity according to Abildgaard.⁷ The antithrombin III activity was expressed as a percentage of normal plasma activity.

Antithrombin III protein concentration was determined by radial immunodiffusion according to Mancini *et al*^{7a} on the M-Partigen agarose plate (Behring Diagnostics).

Statistical comparisons were made by simple linear regression and Student's *t* test for unpaired data.

Results

Glycosylated haemoglobin concentration was increased ($p < 0.001$) and antithrombin III activity decreased ($p < 0.001$) in addicts, while no difference was found in antithrombin III and glucose plasma concentrations (Table). Furthermore, as previously found⁸ there was a good correlation between antithrombin III activity and antithrombin III protein concentration in healthy controls ($r = 0.93$; $p < 0.001$) (Fig. 1), but not in addicts ($r = 0.16$; $p = \text{NS}$) (Fig. 2). No significant correlation was found between antithrombin III activity and glycosylated haemoglobin and plasma glucose concentrations or heroin dose in addicts.

Discussion

Antithrombin III is believed to be one of the major regulator proteins of the coagulation system.⁹ A functional defect has recently been described —

Concentrations of plasma glucose and glycosylated haemoglobin and antithrombin III concentration and activity in opiate addicts and controls

	Addicts (19)	p	Controls (20)
Plasma glucose concentration (mmol/l)	4.58 ± 0.74	NS	4.64 ± 0.81
Glycosylated haemoglobin (%)	7.1 ± 0.15	p < 0.001	6.2 ± 0.18
Antithrombin III activity (%)	87.62 ± 12.23	0.001	104.9 ± 8.94
Antithrombin III concentration (mg/100 ml)	30.72 ± 3.74	NS	31.32 ± 2.35

Results are given as mean ± SD.

Fig. 1 Correlation between antithrombin III activity and antithrombin III protein concentration in healthy controls.

Fig. 2 Correlation between antithrombin III activity and antithrombin III protein concentration in opiate addicts.

antithrombin III Budapest — which is associated with venous thromboembolism,¹⁰ and thromboembolic episodes in opiate addicts have been reported.¹¹

Our data suggest the existence of depressed antithrombin III biological activity in opiate addicts and

may explain the findings of changes in the blood coagulation system in addicts.^{12,13} These changes are similar to those found in diabetics, who have increased platelet aggregation¹⁴ and increased fibrinogen values.¹⁵ Moreover, these data highlight other similarities between opiate addicts and diabetics.^{16,17}

To our knowledge this is the first demonstration that chronic heroin administration interferes adversely with protein biological function. Characterisation of the molecular alteration in antithrombin III in opiate addicts is needed to establish whether the impaired antithrombin III activity is affected, as in diabetics,¹ by altered glucose metabolism.

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Requests for reprints to: Dr Antonio Ceriello, Istituto di Patologia Speciale Medica, I Facoltà di Medicina, Piazza Miraglia — 80138 Naples, Italy.

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