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SHORT COMMUNICATIONS

Effect of Metergoline, a Powerful and Long-Acting Antiserotoninergic Agent, on Insulin Secretion in Normal Subjects and in Patients with Chemical Diabetes

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Summary. The effect of metergoline on insulin secretion has been evaluated in normal subjects and in patients with chemical diabetes. The repeated administration of metergoline, 2 mg at four-hour intervals to give a total of 24 mg, has enhanced insulin secretion in response to i. v. glucose in normal subjects but not in chemical diabetics. No changes in blood glucose pattern were observed. Under similar conditions, metergoline administration caused a slight but significant decrease in arginine-induced insulin release, both in normal subjects and in chemical diabetics. These results support the concept of a serotoninergic control of insulin secretion and suggest that serotonin exerts different effects on insulin release according to the different stimuli.

Key words: Serotonin, 5-hydroxytryptamine, metergoline, arginine, antiserotoninergic drugs, insulin secretion, glucose tolerance test.

In recent years evidence has arisen concerning the existence of a serotoninergic control of insulin (IRI) secretion. However, details of this control remain to be stated, since serotonin (5-HT), present in the pancreatic islets of several animal species [1], has been shown to enhance or to reduce basal as well as glucose-induced IRI release in the experimental animal [2–5]. In human beings, impaired IRI secretion has been observed in the carcinoid syndrome [6, 7], but 5-HT has also been reported to enhance glucose-induced IRI release in normal subjects [2].

In laboratory animals, the experimental use of antiserotoninergic (anti-5-HT) agents has yielded conflicting results, since methysergide, cyproheptadine and cinanserin have been shown to exert different effects in potentiating IRI secretion or in counteracting the inhibitory effect of 5-HT [4].

In human beings, methysergide has been shown to enhance glucose-induced IRI release in adult-onset diabetes mellitus, but not in normal subjects [8], while cyproheptadine has failed to modify IRI response to glucose or to leucine in normal subjects [9].

In the present study we have evaluated the effect of a powerful, specific and long-lasting anti-5-HT agent, metergoline [10, 11], on IRI secretion in normal subjects and in patients with chemical diabetes.

Material and Methods

Twenty seven subjects of normal weight, 13 in good health and 14 with newly-discovered chemical diabetes, volunteered for our study. 6 normal subjects and 6 chemical diabetics, properly matched for age and sex, underwent an i.v. glucose tolerance test (IVGTT) (0.5 g/kg body weight infused over a 3 min period) in basal conditions and after repeated treatment with metergoline (Liserdol®, Farmitalia, 2 mg at 4-h intervals, to give a total dose of 24 mg). In 7 normal subjects and in 8 chemical diabetics an arginine infusion (25 g l-arginine monochloride infused over a 30 min period) was carried out under basal conditions and after a metergoline treatment as described for the IVGTT.

Blood glucose levels were determined by a glucose-oxidase method [12]. Serum IRI was evaluated by radioimmunoassay [13]. Statistical analysis were performed by the Wilcoxon non parametric test.

Results

Fig. 1 shows that following metergoline administration glucose-induced IRI release was significantly enhanced in normal subjects; differences were statistically significant at 40 and 50 min ($p<0.05$) and when the IRI areas (described by the IRI curves above fasting IRI values) are considered ($p<0.05$). In chemical diabetics, IRI secretion was not affected by the drug. The glucose disappearance rate was not significantly affected by the repeated metergoline administration, mean values of K_G [14] being 3.04 ± 0.84 and 3.13 ± 0.81 in normal subjects, and 0.93 ± 0.16 and 1.28 ± 0.16 in chemical diabetics.

Fig. 2 shows that arginine-induced IRI release was reduced by metergoline treatment both in normal subjects and in chemical diabetics, while blood glucose pattern was not modified by the drug. The IRI area was reduced in 6 normal subjects ($p < 0.05$) and in 7 chemical diabetics ($p = 0.02$). As far as the single points of the IRI curves are considered, only the 60 min value was lessened after metergoline treatment in 6 chemical diabetics ($p < 0.01$).

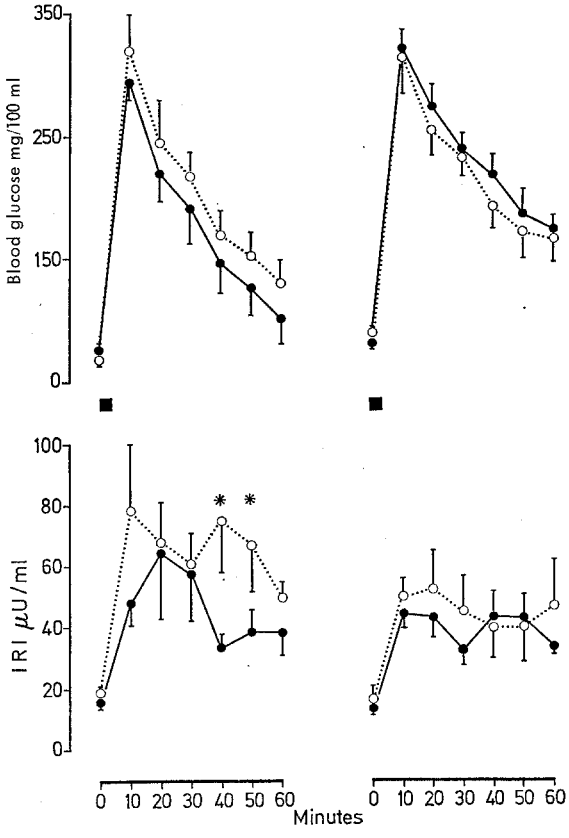

Fig. 1. Blood glucose and serum IRI levels following i.v. glucose in normal subjects (left diagram) and chemical diabetics (right diagram) in basal conditions (●———●) and after repeated metergoline administration (2 mg at 4 h intervals to give a total of 24 mg) (O·····O). Vertical bars indicate ± SEM. The dark square indicates glucose infusion. * $p < 0.05$

to be responsible for the significantly increased IRI secretion. Our results support previous findings in the experimental animal of a potentiation of glucose-induced IRI release by anti-5-HT agents and of an inhibition of IRI secretion by exogenous 5-HT. On the other hand, in our chemical diabetics IRI release was not affected by metergoline. As a whole, our results are in opposition with those of Quickel *et al.* [8], who have shown a potentiating effect of methysergide on glucose-induced IRI release in diabetic subjects but not in the normals. In considering normal subjects, differences are difficult to explain, though metergoline has been shown to exert a longer and a stronger [10,

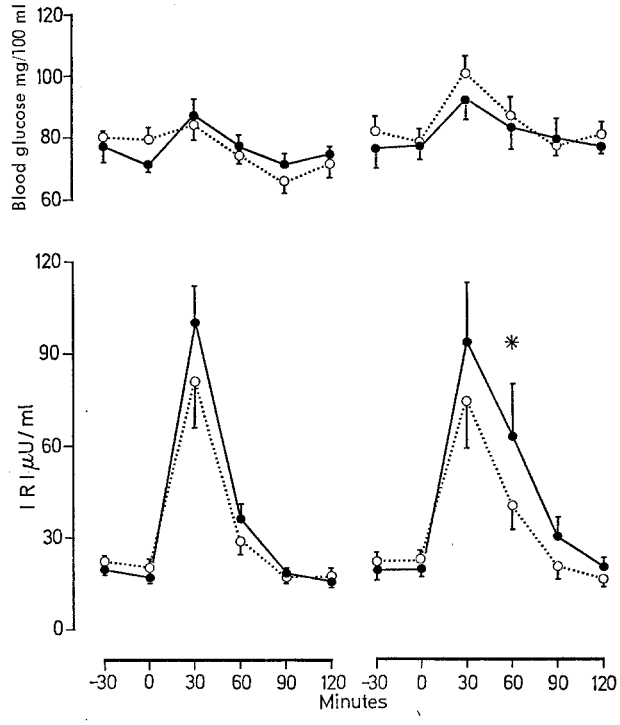

Fig. 2. Blood glucose and serum IRI levels in response to arginine infusion in normal subjects (left diagram) and chemical diabetics (right diagram) in basal conditions (●———●) and after repeated metergoline administration (as in Fig. 1.) (O·····O). Vertical bars indicate ± SEM. * $p < 0.01$

Discussion

In the present study we have shown that metergoline, a specific and longlasting anti-5-HT agent enhanced glucose-induced IRI release in normal subjects. Following metergoline administration, blood glucose levels were slightly higher (+ 11.4%) than in basal conditions: this difference, however, is not statistically significant and therefore does not seem

11, 15, 16] anti-5-HT effect than methysergide. In considering diabetic patients, the different effect observed by us and Quickel may be due to the fact that our study was confined to chemical diabetics, while Quickel *et al.* have studied clinically diabetic patients.

Arginine-induced IRI release was slightly but significantly reduced both in normal subjects and in chemical diabetics following metergoline treatment. This result, compared with the effect of metergoline

on IRI response to glucose, appears quite surprising and at present inexplicable. We may only bear in mind that arginine and glucose have been suggested to stimulate IRI secretion in different ways: arginine potentiates insulin response to glucose [18], and its insulinogenic effect is not dependent on metabolism within the B-cell [17]; in addition, phentolamine, an α-blocking agent, has been shown to exert *in vitro* the opposite effect on glucose- and arginine-stimulated IRI release [19]. From this point of view, the opposite effect of metergoline on IRI response to two different stimuli does not appear paradoxical, but rather supports previous results suggesting the existence of different mechanisms for the stimulation of insulin secretion.

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