susceptible heterodimers by age at onset (4.8 % in the age group 0–9, 21.7 % in the age group 20 years or over). The highest odds ratio (OR) was found in patients aged 0–9 years, able to generate 4 heterodimers (OR 161.3, 95 % CI 39.3–662.7).

Therefore, our study confirms on a well-defined population-based cohort an age-dependent gradient of *DQA1* and *DQB1* susceptibility genes. In addition we found a higher prevalence of patients able to generate 0 heterodimers in adult-onset than in childhood-onset diabetes. In different populations, patients able to generate 0 heterodimers are at lower risk than those with 4 heterodimers. Inefficiency in the interaction between peptide antigens and HLA class II molecules are probably involved in these findings. Structural and functional analysis of the HLA class II susceptibility genes has been carried out and molecular mechanisms have been suggested for several of the key steps in the autoimmune insulitis [6]. Our finding of lower prevalence of susceptible heterodimers in adult-onset than in childhood-onset Type I diabetes could suggest either the involvement of other loci in the genetic susceptibility of the disease in adults or heterogeneity of environmental determinants by age at onset of the disease.

Yours sincerely,
Bruno G, Arcari R, Pagano A, Cerutti F, Berrino M, Pagano G

References

1. Mølbak AG, Christau B, Marner B, Borch-Johnsen K, Nerup J (1994) Incidence of insulin-dependent diabetes mellitus in age-groups over 30 years in Denmark. Diabet Med 11: 650–655
2. Bruno G, Merletti F, De Salvia A et al. (1997) Comparison of incidence of insulin-dependent diabetes mellitus in childhood and young adults in the Province of Turin (Italy), 1984–91. Diabet Med 14: 964–969
3. Vandewalle CL, Decraene T, Schuit FC et al. (1993) Insulin antibodies and high titre cell antibodies are preferentially associated with the HLA DQA1*0301-DQB1*0302 haplotype at clinical onset of Type I (insulin-dependent) diabetes mellitus before age 10 years, but not at onset between age 10 and 40 years. Diabetologia 36: 1155–1162
4. Lohman T, Seissler J, Verlohren H-J et al (1997) Distinct genetic and immunological features in patients with onset of IDDM before and after age 40. Diabetes Care 20: 524–529
5. Horton V, Stratton I, Bottazzo GF et al (1999) Genetic hetrogeneity of autoimmune diabetes: age of presentation in adults is influenced by HLA DRB1 and DQB1 genotypes (UKPDS 43). Diabetologia 42: 608–616
6. Nepom GT, Kwok WW (1998) Molecular basis for HLA-DQ associations with IDDM. Diabetes 47: 1177–1184
7. Caillat ZS, Garchon HJ, Timsin J et al (1992) Age-dependent HLA genetic heterogeneity of Type I insulin-dependent diabetes mellitus. J Clin Invest 90: 2242–2250
8. Bruno G, De Salvia A, Arcari R et al (1999) Clinical, immunological and genetic heterogeneity of diabetes in an Italian population-based cohort of lean newly-diagnosed patients aged 30–54 yrs. Diabetes Care 22: 50–55

Insulin-dependent diabetes mellitus induced by the antitussive agent dextromethorphan

Dear Sir,
In animal studies, antagonists of the *N*-methyl-D-aspartate (NMDA) receptor, which is a subtype of ionotropic glutamate receptors, are neuroprotective in focal cerebral ischaemia and therefore became a hot topic in brain research [1, 2]. Dextromethorphan, a widely used antitussive agent, has non-competitive antagonistic effects at the NMDA receptor [3].

In our clinic a prospective double-blind placebo-controlled study was initiated to evaluate a possible beneficial effect of high-dose dextromethorphan in children with severe bacterial meningitis [4]. So far four patients have been included in this study. Surprisingly, two of them developed Type I (insulin-dependent) diabetes mellitus during dextromethorphan treatment. Because of this unexpected serious adverse event, the patients were unblinded: both of the diabetic patients received dextromethorphan, whereas the other two patients received placebo.

Patient 1. A 10-year-old boy was admitted to the intensive care unit because of severe bacterial meningitis. Within 24 h high-dose dextromethorphan treatment (36 mg · kg^{-1} · day^{-1}, in 4 doses) given by nasogastric tube was initiated. After 5 days blood glucose began to rise up to 20 mmol/l and he developed ketoacidosis. Laboratory analysis showed an appreciable decrease in insulin serum concentration despite a high blood glucose concentration (insulin serum concentration 65 pmol/l, blood glucose concentration 21.9 mmol/l at the same time). Treatment with regular insulin was initiated. Up to 3 units of regular insulin per kilogram body weight a day were necessary to keep blood glucose in the normal range. Dextromethorphan was reduced stepwise over the next 4 days and then stopped. After another 3 days insulin doses could be reduced considerably and within 1 day the insulin treatment could be stopped (Fig. 1). The patient received prednisolon, which was stopped 1 day before insulin treatment became necessary. A year later the patient's glucose metabolism is still normal.

Patient 2. A 14-year-old girl was admitted to the intensive care unit because of severe meningoencephalitis. Within 24 h high-dose dextromethorphan treatment (36 mg · kg^{-1} · day^{-1}, in 4 doses) given by nasogastric tube was initiated. After 2 days her blood glucose concentration began to rise up to 20 mmol/l. Treatment with regular insulin was initiated and up to 3 units of regular insulin were necessary to return her blood glucose to the normal concentration. No laboratory analysis was available to document a decreased insulin secretion. Dextromethorphan was reduced stepwise over the next 4 days and then stopped. After another 2 days insulin doses decreased considerably and could be stopped. The patient received dexametha-

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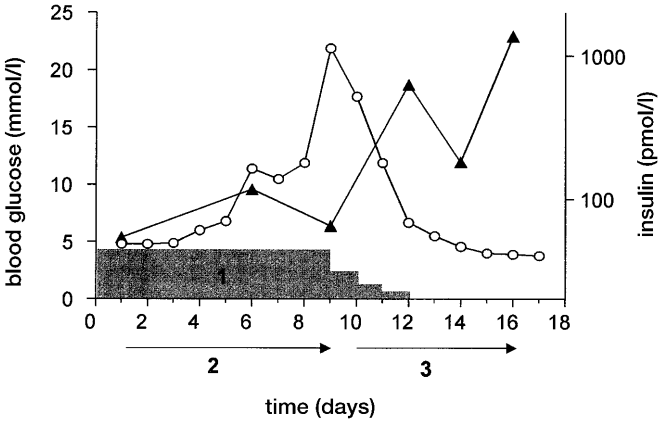

Fig. 1. ▲ insulin serum concentrations in pmol/l (logarithmic scale), o blood glucose concentrations in mmol/l (insulin serum concentration and blood glucose concentration measured the same time) Duration of high-dose dextromethorphan treatment (**1**), prednisolon treatment (**2**), and insulin treatment (**3**)

sone, which was stopped two days after cessation of insulin treatment. Now, 6 months later, glucose tolerance remains normal.

Retrospectively, in four other children treated with high doses of dextromethorphan because of encephalitis (1 patient), status epilepticus (2) or severe brain injury (1) increased glucose concentrations were observed after the initiation of treatment with dextromethorphan. In one of these patients decreased insulin secretion was documented (insulin serum concentration 57 pmol/l during a blood glucose concentration of 10.5 mmol/l). None of the children needed insulin treatment. Blood glucose concentration returned to normal after reduction or cessation of dextromethorphan treatment.

Our findings show that dextromethorphan treatment induced insulin-dependent diabetes in these children. In animal experiments, NMDA receptors were identified in pancreatic beta cells in rats. Their stimulation by NMDA was able to enhance glucose-induced insulin secretion [5]. We therefore hypothesise, that high doses of dextromethorphan inhibit insulin secretion by antagonism of the NMDA receptor leading to deterioration of glucose metabolism. Moreover, in rat pancreatic beta cell stimulation of the NMDA receptor leads to a rise in the intracellular calcium concentration [6]. In cortical neurons of fetal rats, dextromethorphan was shown to inhibit voltage-operated calcium channels. Notably, in these experiments, the NMDA receptor ion channel could be blocked by much lower concentrations of dextromethorphan than the voltage-gated calcium channel [7]. Taking this into account, inhibition of voltage-gated calcium channels by dextromethorphan could also play a part in rat or human beta-cells and contribute to the observed inhibition of insulin secretion in the patients described although this mechanism seems to be less probable because of the much higher concentrations needed.

Both patients received glucocorticoids which are known to induce peripheral insulin resistance. If they were solely responsible for the hyperglycaemia observed, increased insulin secretion would be expected in our patients. The insulin secretion was, however, blocked, making it unlikely that glucocorticoids were the primary cause for the acute diabetes mellitus observed. Nevertheless glucocorticoid-induced insulin-resistance could have aggravated the hyperglycaemia and could be responsible for the high doses of insulin needed to stabilise blood glucose concentrations in the normal range in the patients described.

Abnormal glucose metabolism has not been reported so far in patients receiving dextromethorphan at low doses as used in antitussive agents (1–2 mg · kg^{-1} · day^{-1}).

Apart from the possible neuroprotective effect of NMDA receptor antagonists in the damaged brain discussed above, blockade of NMDA receptors was recently shown to induce apoptotic neurodegeneration in the developing rat brain [8]. If a similar process occurs in beta cells which share many commonalties with brain cells, the question has to be answered, if NMDA receptor antagonists administered during a vulnerable period might play a part in triggering beta-cell destruction leading to Type I diabetes in genetically susceptible humans.

We conclude that Type I diabetes can occur as a side effect in children treated with high doses of dextromethorphan, which most likely inhibits insulin secretion in beta cells by NMDA receptor antagonism. Careful monitoring of blood glucose during such a therapy is therefore mandatory.

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Yours sincerely,
D. Konrad, D. Sobetzko, B. Schmitt, E. J. Schoenle

References

1. Rothman SM, Olney JW (1986) Glutamate and the pathophysiology of hypoxic-ischemic brain damage. Ann Neurol 19: 105–111
2. Steinberg GK, Yoon EJ, Kunis DM, Sun GH, Maier CM, Grant GA (1995) Neuroprotection by N-methyl-D-aspartate antagonists in focal cerebral ischemia is dependent on continued maintenance dosing. Neuroscience 64: 99–107
3. Choi DW, Peters ST, Viseskul V (1987) Dextrorphan and levorphanol selectively block N-methyl-D-aspartate receptor-mediated neurotoxicity on cortical neurons. J Pharmacol Exp Ther 242: 713–720
4. Schmitt B, Wohlrab G, Steinlin M, Fanconi S, Nadal D, Boltshauser E (1998) Treatment with the N-methyl-D-aspartate antagonist dextromethorphan in severe bacterial meningitis: preliminary results. Eur J Pediatr 157: 863–865
5. Molnar E, Varadi A, McIlhinney RAJ, Ashcroft SJH (1995) Identification of functional ionotropic glutamate receptor proteins in pancreatic β-cells and islets of Langerhans. FEBS Lett 371: 253–257
6. Inagaki N, Kuromi H, Gonoi T, et al. (1995) Expression and role of ionotropic glutamate receptors in pancreatic islet cells. FASEB J 9: 686–691
7. Trube G, Netzer R (1994) Dextromethorphan: cellular effects reducing neuronal hyperactivity. Epilepsia 35[Suppl 5]:S62–S67
8. Ikonomidou C, Bosch F, Miksa M, et al. (1999) Blockade of NMDA receptors and apoptotic neurodegeneration in the developing brain. Science 283: 70–74