EFFECT OF LONG-TERM TREATMENT WITH SODIUM VALPROATE ON GONADOTROPHIN AND PROLACTIN SECRETION IN PAEDIATRIC PATIENTS

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1 Luteinizing hormone (LH), follicle stimulating hormone (FSH) and prolactin levels were measured in twenty paediatric patients receiving sodium valproate (30 mg/kg body weight daily) and in ten control subjects under control conditions and following LRH-TRH administration. In addition, baseline GH levels were measured in the two groups.

2 No significant differences were observed between the basal and stimulated hormone levels in the two groups. Although sodium valproate may act as anticonvulsant by increasing GABA levels in the central nervous system, the present data indicate that a central GABAergic pathway is probably not involved in the control of gonadotrophin and prolactin secretion.

Introduction

In recent years the rôle exerted by γ -aminobutyric acid (GABA) in the control of anterior pituitary secretion has been extensively investigated. Although still controversial, experimental studies indicate that GABA may play a rôle in the regulation of prolactin, growth hormone (GH), ACTH and luteinizing hormone (LH) secretion (Pass & Ondo, 1977; Ondo, 1974; Grandison & Guidotti, 1979; Takahara *et al.*, 1980; Makara & Stark, 1974). In humans, administration of high doses of GABA, or the GABA-mimetic drug, baclofen, is able to interfere with prolactin and GH release (Koulu, Lammintausta & Dahlstrom, 1979; Cavagnini *et al.*, 1980).

Sodium valproate is commonly employed as an anticonvulsant drug and, though not completely understood, it is thought that it acts by enhancing the central GABAergic tone, due to inhibition of GABA transaminase (Pinder *et al.*, 1977; Godin *et al.*, 1969). We studied the effects of long-term treatment with sodium valproate on the pituitary responsiveness to stimulation with synthetic luteinizing hormone releasing hormone (LRH) and thyrotrophin releasing hormone (TRH) in paediatric patients receiving the drug to prevent febrile convulsions.

Methods

Twenty patients with febrile convulsions, 12 males and 8 females aged 20 to 36 months and 5 male and 5

female subjects of comparable age and weight entered this study. All the patients had been receiving sodium valproate (30 mg/kg body weight daily) for 8 to 16 months to prevent recurrence of febrile seizures. Purposes and details of the study were explained to the parents who gave their consent. Studies started at 08.00 h on fasting, recumbent subjects. A 21-gauge scalp vein needle was inserted in a cubital vein and patency achieved by a slow infusion of normal saline. After collection of two baseline samples (–15 and 0 min) all subjects received an i.v. bolus of 50 μ g synthetic LRH (Relisorm, Serono) plus 200 μ g synthetic TRH (Relefact, Hoechst). Additional blood samples were collected in heparinized tubes 30, 60 and 120 min thereafter. Blood was immediately centrifuged and plasma stored at –20°C until required. All samples from each subject were processed in duplicate in the same assay. LH and FSH levels were measured by specific RIA methods; all the reagents were obtained from Biodata, Milan, Italy. The methods are sensitive to about 1 mIU/ml. Intra- and interassay variations were 3.5 and 8% for LH; 4.3 and 7.5% for FSH respectively. The results are reported as mIU/ml of the 2nd IRP-HMG. Prolactin was assayed by a double-antibody method, sensitive to about 1 ng/ml. Standard, antiserum and ¹²⁵I-labelled human prolactin were obtained from Biodata. Intra- and interassay variations were 4 and 7.5% respectively. One nanogram Biodata antigen corresponds to 23 μ u WHO 71/222. Plasma GH was assayed by a RIA

Figure 1 Plasma LH and FSH levels in 20 patients receiving sodium valproate (●) and in 10 control subjects (○) under control conditions and in response to i.v. 50 µg synthetic LRH administration. Mean ± s.e. mean results.

method using reagents from Biodata. This method ensures assays of about 0.1 ng/ml with intra- and interassay variations of 4.5 and 11% respectively. One nanogram of the employed antigen corresponds to 2 µU WHO 66/217. The two-tailed, paired and unpaired Student's *t*-tests were used for a statistical analysis of the data. All the results are reported as means ± s.e. mean.

Results

The results are reported in Figure 1 and Table 1.

Under control conditions, the patients had average LH and FSH levels of 3.55 ± 0.56 mIU/ml and 1.99 ± 0.35 mIU/ml respectively at time 0. This was not statistically different from the values of 3.48 ± 0.28 and 2.07 ± 0.25 mIU/ml for LH and FSH respectively seen in the control subjects. Administration of 50 µg synthetic LRH induced a prompt increase in gonadotrophin levels in both groups. In the patients, peak values observed at time +30 min were 13.05 ± 3.71 and 7.74 ± 1.63 mIU/ml for LH and FSH. These values were not significantly different from the values of 12.93 ± 3.04 mIU/ml for LH and 9.78 ± 1.63 mIU/ml for FSH observed at the same time in the control subjects ($P > 0.05$). All the peak values were significantly higher than baseline ($P < 0.001$). No significant statistical difference was found by evaluating any of the results in relation to the sex of the subjects (unreported data). Prolactin levels were similar in both groups: 13.08 ± 1.77 ng/ml and 13.84 ± 2.92 ng/ml in the patients and controls respectively.

TRH administration induced a clear-cut increase in prolactin. Average peak values were observed at time +30 min: 41.43 ± 5.84 ng/ml and 52.23 ± 7.08 ng/ml in patients and controls respectively. These values were significantly higher than baseline ($P < 0.001$), but not significantly different ($P > 0.05$). Baseline GH levels recorded in the two groups were 1.16 ± 0.29 and 1.68 ± 0.75 ng/ml in patients and controls respectively. No significant modifications were observed following LRH-TRH administration ($P > 0.05$). No side effects were observed during the study.

Discussion

The data of the present study indicate that treatment with sodium valproate for periods up to 16 months is unable to interfere with gonadotrophin and prolactin secretion; moreover, gonadotrophin and prolactin

Table 1 Plasma prolactin levels (ng/ml) in 20 patients receiving sodium valproate and in 10 control subjects under control conditions and in response to i.v. 200 µg synthetic TRH administration. Mean ± s.e. mean results.

	Time (min)				
	-15	0	+30	+60	-120
Patients					
Mean	15.46	13.98	41.33	27.31	16.28
s.e. mean	1.99	1.77	5.84	4.63	2.07
Controls					
Mean	13.90	13.84	52.33	32.93	17.35
s.e. mean	2.36	2.92	7.08	5.04	2.23

responsiveness to LRH-TRH is uninfluenced by the drug. Since sodium valproate may act by enhancing the central GABAergic tone (Godin *et al.*, 1969), our data indicate that GABA, or a GABAergic pathway, plays presumably little or no part in the control of gonadotrophin and prolactin secretion. This is in agreement with our observation that short-term treatment with baclofen, a GABA-mimetic drug (Fehr & Bein, 1974; Anden & Wachtel, 1977) is devoid of any effect on baseline and stimulated gonadotrophin and prolactin secretion (unpublished data). We have shown that low doses of GABA are not able to interfere with prolactin and GH secretion in man (Masala *et al.*, 1978). However, interference with prolactin and GH has been reported to occur if higher doses are used (Cavagnini *et al.*, 1980). Similarly, administration of baclofen or γ -hydroxybutyric acid modifies these hormones in man (Koulu *et al.*, 1979; Cavagnini *et al.*, 1977; Takahara *et al.*, 1977). It should be noted, however, that some authors attribute prolactin inhibiting action to GABA (Schally *et al.*, 1977) and that sodium valproate has been shown capable of blunting the GH re-

leasing stimulus exerted by diazepam in man (Koulu *et al.*, 1979). As for gonadotrophin secretion, experimental studies indicate that, by acting on structures other than the pituitary, GABA releases LH but not FSH (Ondo, 1974; Pass & Ondo, 1977). In view of these discrepancies on the endocrine effects of GABA, it may be that the enhanced central GABAergic tone due to sodium valproate is not sufficient to interfere with anterior pituitary function, whereas high doses of GABA are. We have recently demonstrated that children receiving phenobarbitone to prevent febrile convulsions have low baseline gonadotrophin levels and an impaired response to LRH (Masala *et al.*, 1980). Although it may have other side effects (Batalden, van Dyne & Cloyd, 1979; Willmore, Wilder & Bruni, 1978; Fichsel & Knöpfle, 1978) sodium valproate seems to be devoid of any action on gonadotrophin and prolactin secretion in children.

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References

- ANDEN, N.E. & WACHTEL, H. (1977). Biochemical effects of baclofen (parachloro phenyl-GABA) on the dopamine and noradrenaline in the rat brain. *Acta Pharmac. Tox.*, **40**, 310–316.
- BATALDEN, B.P., VAN DYNE, B.J. & CLOYD, J. (1979). Pancreatitis associated with valproic acid therapy. *Pediatrics*, **64**, 520–521.
- CAVAGNINI, F.C., INVITTI, C., DI LANDRO, A., TENCONI, L., MARASCHINI, C. & GIROTTI, G. (1977). Effects of a gamma aminobutyric acid (GABA) derivative, baclofen, on growth hormone and prolactin secretion in man. *J. clin. Endocrinol. Metab.*, **45**, 579–584.
- CAVAGNINI, F., INVITTI, C., PINTO, M., MARASCHINI, C., DI LANDRO, A., DUBINI, A. & MARELLI, A. (1980). Effect of acute and repeated administration of gamma-aminobutyric acid (GABA) on growth hormone and prolactin secretion in man. *Acta Endocrinol.*, **93**, 149–154.
- FEHR, H.U. & BEIN, H.J. (1974). Sites of action of a new muscle relaxant (baclofen, Lioresal, Ciba 34647-Ba). *J. int. med. Res.*, **2**, 36–40.
- FICHSEL, H. & KNÖPFLE, G. (1978). Effects of anticonvulsants on thyroid hormones in epileptic children. *Epilepsia*, **19**, 323–328.
- GODIN, Y., HEINER, L., MARK, J. & MANDEL, P. (1969). Effects of di-n-propylacetate, an anticonvulsive compound, on GABA metabolism. *J. Neurochem.*, **16**, 869–873.
- GRANDISON, L. & GUIDOTTI, A. (1979). γ -aminobutyric acid receptor function in rat anterior pituitary: evidence for a control of prolactin release. *Endocrinology*, **105**, 754–759.
- KOULU, M., LAMMINTAUSTA, R., KANGAS, L. & DAHLSTROM, S. (1979). The effect of methysergide, pimozone and sodium valproate on the diazepam-stimulated growth hormone secretion in man. *J. clin. Endocrinol. Metab.*, **48**, 119–122.
- KOULU, M., LAMMINTAUSTA, R. & DAHLSTROM, S. (1979). Stimulatory effect of acute baclofen administration on human growth hormone secretion. *J. clin. Endocrinol. Metab.*, **48**, 1038–1040.
- MAKARA, G.B. & STARK, E. (1974). The effects of gamma-aminobutyric acid (GABA) and GABA antagonist drugs on ACTH release. *Neuroendocrinology*, **16**, 178–183.
- MASALA, A., DELITALA, G., DEVILLA, L., ALAGNA, S. & ROVASIO, P.P. (1978). Effects of gamma aminobutyric acid (GABA) on growth hormone and prolactin secretion in man. *I.R.C.S. Med. Sci.*, **6**, 200.
- MASALA, A., MELONI, T., ALAGNA, S., ROVASIO, P.P., MELE, G. & FRANCA, V. (1980). Pituitary responsiveness to gonadotrophin releasing and thyrotrophin releasing hormones in children receiving phenobarbitone. *Br. med. J.*, **281**, 1175–1177.
- ONDO, J.G. (1974). Gamma-aminobutyric acid effects on pituitary gonadotropin secretion. *Science*, **186**, 738–739.
- PASS, K.A. & ONDO, J.G. (1977). The effects of γ -aminobutyric acid on prolactin and gonadotropin secretion in the unanesthetized rat. *Endocrinology*, **100**, 1437–1442.
- PINDER, R.M., BROGDEN, R.N., SPEIGHT, T.M. & AVERY, G.S. (1977). Sodium valproate: a review of its pharmacological properties and therapeutic efficacy in epilepsy. *Drugs*, **13**, 81–123.
- SCHALLY, A.V., REDDING, T.W., ARIMURA, A., DUPONT,

- A. & LINTICHUM, G.L. (1977). Isolation of gamma aminobutyric acid from pig hypothalami and demonstration of its prolactin release inhibiting (PIF) activity *in vivo* and *in vitro*. *Endocrinology*, **100**, 681–691.
- TAKAHARA, J., YUNOKI, S., YAKUSHIJI, W., YAMANE, Y. & OFUJI, T. (1977). Stimulatory effects of gamma hydroxybutyric acid on growth hormone and prolactin release in humans. *J. clin. Endocrinol. Metab.*, **44**, 1014–1017.
- TAKAHARA, J., YUNOKI, S., HOSOGY, H., YAKUSHIJI, W., KAGEYAMA, J. & OFUJI, T. (1980). Concomitant increase in serum growth hormone and hypothalamic somatostatin in rats after injection of γ -aminobutyric acid, aminooxyacetic acid, or γ -hydroxybutyric acid. *Endocrinology*, **106**, 343–347.
- WILLMORE, L.J., WILDER, B.J. & BRUNI, J. (1978). Effect of valproic acid on hepatic function. *Neurology*, **28**, 961–963.

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