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Rabbit model simulating transient hyperglycinemia following transurethral prostatectomy

P. Gentens[1], P. P. De Deyn[2], R. D'Hooge[2], H. Pei[2], M.-J. Tassignon[3], S. Van Dromme[1], and B. Marescau[2]

[1] Department of Urology, [2] Laboratory of Neurochemistry and Behavior and Department of Neurology A.Z. Middelheim, O.C.M.W. Medical Research Foundation, and [3] Department of Ophtalmology, University of Antwerp (U.I.A.), Antwerp, Belgium

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Summary. Glycine was intravenously injected in rabbits and resulted in a dose dependent hyperglycinemia. A dose of 10mmol/kg was sufficient to achieve plasma levels of 10 to 16mM comparable to serum levels in patients at the end of a transurethral prostatectomy. The experiments documented that hyperglycinemia is associated with a significant increase of this substance in tissues outside the plasma compartment. Glycine loading resulted in a tenfold elevation of this amino acid in cerebrospinal fluid 10 minutes after injection. In retina and vitreous humor a five- to tenfold increase in glycine content was observed at 10 minutes post injection while in the anterior chamber fluid the maximum increase appeared at 30 minutes.

Significant increases of the glycine content were found in different cerebral structures at 30 minutes post administration.

The significant elevations of this neurotransmitter within the central nervous system are prerequisites for possible toxic side effects in the course of transurethral prostatectomy (TURP). Hyperglycinemia might be involved in the pathogenesis of visual disturbances following transurethral prostatectomy and the other neurological complications of TURP syndrome. Our observations add more evidence to this hypothesis.

Keywords: Amino acids – Transurethral prostatectomy – Transurethral prostatectomy syndrome – Hyperglycinemia – Animal model

Introduction

Almost 50 years ago, glycine solutions were introduced as irrigating fluid for endoscopic surgery in urology (Nesbit et al., 1948). Absorption of irrigating fluid takes place in every patient undergoing transurethral prostatectomy (Norlen et al., 1986; Hahn et al., 1988; Hulten et al., 1991). The glycine

solution enters directly into the circulation through venous lacerations or may accumulate in the perivesical space (Oester et al., 1969). The absorbed glycine causes temporary hyperglycinemia. Sometimes, very high peak concentrations of glycine are measured in plasma at the end of endoscopic prostatectomy with values up to 16 mM (normal values: 0.160–0.600 mM).

In the nervous system, glycine binds at two receptor sites: one sensitive to strychnine, associated with an inhibitory chloride channel, and mainly situated in spinal cord (Gly_A receptor), and another insensitive to strychnine, associated with the excitatory N-methyl-D-aspartate receptor complex, and mainly localised in supraspinal areas (Gly_B receptor) (Werman et al., 1967, 1968; Aprison et al., 1978; Compton et al., 1990; Thomson et al., 1989).

A complication, unique to patients who undergo transurethral prostatectomy (TURP) is the transurethral prostatectomy syndrome (TURP syndrome). This syndrome was originally described by Creevy (1948). Absorption of distilled water, used as irrigating fluid at that time, caused intravascular hemolysis. Hemolysis was regarded as the main etiologic mechanism in the pathogenesis of TURP syndrome. The use of nearly isotonic solutions diminished the incidence of this specific complication, but an awkward and complex clinical syndrome still occurs with an incidence of 1.5 to 4% (Henderson et al., 1980; Ellis et al., 1991). Initial symptoms of this TURP syndrome are restlessness and confusion. Hypotension with bradycardia are characteristic for this complication although temporary elevation of blood pressure may be noted in an early phase. Other symptoms of this syndrome are vomiting, shortness of breath and convulsions. Severe cases may present coma, cardiac dysrhythmia, respiratory arrest and renal failure (Ghanem et al., 1990). Visual disturbances form another complication associated with transurethral prostatectomy. Temporary blindness following an endoscopic prostatectomy is reported by several authors (Defalque et al., 1975; Appelt et al., 1979; Kaiser et al., 1985; Hahn, 1988; Cashman, 1990; Russell, 1990).

Different and confusing hypotheses about the pathogenesis of the actual TURP syndrome continue to exist among which dilutional hyponatremia, hyperammonemia and volumetric overload. Glycine toxicity was not directly considered in the pathophysiology of TURP syndrome. The study of Mizutani et al. (1990) however suggested a link between hyperglycinemia and visual disturbances associated with TURP. Experimental work by Wang et al. (1989) also indicated glycine as a candidate substance responsible for this complication.

In order to investigate the pathophysiologic influence of temporary hyperglycinemia associated with TURP, an animal model was elaborated and glycine concentrations measured in cerebral tissue and body fluids.

Materials and methods

Experimental animals

Prior to the experiments, male and female rabbits of the strain "de witte van Dendermonde" were housed under standard environmentally controlled conditions (12-h light-dark cycle, constant room temperature and humidity).

Glycine loading and dose dependent plasma levels

The aim was to achieve plasma glycine levels between 10 and 16 mM over a period of at least 30 minutes comparable to the plasma levels observed at the end of endoscopic prostatectomy in man. Therefore, in a dose-finding test, we injected different glycine doses in a series of animals. Glycine was dissolved in 0.9% NaCl at different concentrations (140, 350, 800 and 1,000 mM). Each animal received 10 ml/kg of the respective glycine solution. Glycine solutions were injected in a vein of one ear and approximately 0.5 ml blood was drawn from a vein of the other ear at regular time intervals (0, 10, 20, 30, 40, 60, 90, 120, 180, 240, 360, 480 min after injection). Plasma samples were obtained by centrifugation at 2,200 × g for 10 min. Injection of glycine doses of 1.4, 3.5 and 8 mmol/kg resulted in plasma glycine levels lower than 8 mM already after 30 min. A loading dose of 10 mmol/kg achieved our goal and this dose was used in all further experiments.

Glycine levels in cerebrospinal fluid after glycine loading

10 mmol/kg glycine was injected intravenously and an equal volume 0.9% NaCl was injected in the control group. Cerebrospinal fluid (100 to 200 μl) was sampled by suboccipital puncture under Hypnorm® (Janssen Pharmaceutica) anesthesia (1 ml/kg) at 10, 20 or 30 min after glycine injection. Each sample was obtained from a different animal. Traumatic samples as judged by microscopic examination were excluded for analysis.

Glycine levels in cerebral tissue and in ocular structures after glycine loading

The anesthesized animals were killed (by bleeding) at the appropriate time following glycine injection (10, 30 min). Control rabbits were injected with saline. The skull was opened and the cerebrum removed immediately, rinsed in ice cold 0.9% NaCl solution and stored at −75°C until dissection and amino acid analysis; 100 to 200 mg tissue (wet weight) was taken from different regions: spinal cord, medulla oblongata, pons, mesencephalon, hypothalamus, thalamus, hippocampus, striatum, cerebellum, frontal cortex and occipital cortex. The eyes were also excised immediately after sacrificing the animals. Anterior chamber fluid, vitreous humor and retino-choroid tissue were collected for glycine determination.

Amino acid analysis

Glycine levels were determined using a Biotronik LC 6001 amino acid analyzer (Biotronik, D-6457 Maintal, Germany). The amino acids were separated by liquid column chromatography over a cation exchange resin, BTC 2710 (Biotronik, D-6457 Maintal, Germany), and detected by the colorimetric ninhydrin method. A conventional elution program for the analysis of amino acids in physiological fluids was followed, except that after the elution of methionine the column was washed with 0.3 N LiOH. A resin bed height of 140 mm was used. After injection of the sample a 0.12 N lithium citrate buffer (pH 2.67) was pumped during 17 min with a column temperature of 35.5°C. During 36 min, 0.13 N lithium citrate buffer (pH 3.05) was pumped at the same column temperature. Next 5 min the same buffer was pumped at a column temperature of 49°C. With the same column temperature 0.20 N lithium citrate buffer (pH 3.61) was pumped during 20 min. In a following step the resin was washed with 0.3 N LiOH and equilibrated with starting buffer just before the next analysis. Buffer and ninhydrin flow rate was 20 ml/h. Recovery for glycine was 98%, day-to-day analyses have shown coefficients of variation of 0.77.

Sample preparation

Plasma samples were deproteinized with 10% sulfosalicylic acid solution: 200 μl plasma were vortexed with 50 μl sulfosalicylic acid solution. Proteins were precipitated

with a Beckman microfuge (Beckman Instruments, Fullerton, CA) at 8,000 × g. Clear supernatant was diluted with sample buffer (0.12N lithium citrate buffer, pH 2.20), depending on glycine loading and time after loading, and used for glycine determination.

Cerebrospinal fluid and anterior chamber fluid were deproteinized with solid sulfosalicylic acid (1.5mg/100μl sample) and centrifuged like the plasma samples. Again, the dilution with sample buffer depended on glycine or saline loading and time after loading.

Vitreous humor was first filtered by centrifugation over an Amicon Centriflo membrane (type CF25) at 1,000 × g, 6°C and further deproteinized with solid sulfosalicylic acid (1.5mg/100μl).

Brain tissue as well as retino-choroid tissue were homogenized in 1ml 0.5N perchloric acid with a "tissue tearor" (Biospec Products, Bartlesville, USA), model 985. The probe was washed again with 1ml destilled water. After centrifugation (100,000 × g for 30min at 6°C) the clear supernatant was used for analysis.

Materials

Glycine was used as standard for the glycine determination and was purchased from Sigma Chemical Co. (St. Louis, USA). All the other chemicals used for sample perparation and the amino acid analysis were from Merck (Darmstadt, Germany) and were of analytical grade.

Statistics

The glycine levels were given as mean values ± standard deviations. The results were further analyzed by Mann-Whitney U test.

Results

Time-dependent plasma glycine concentrations after intravenous glycine loading

Figure 1 depicts the time-dependent plasma concentrations of glycine in rabbits following a 10mmol/kg intravenous administration of glycine. Plasma levels of glycine rose from 0.67 ± 0.16mM at time 0 to 23.3 ± 0.16mM at ten minutes (n = 5). From then on, plasma levels gradually decreased to reach levels comparable to control after six hours. Until 40minutes after intravenous administration of glycine, plasma concentrations remained at levels above 10mM.

The elimination time in animals seemed to be shorter than in humans: mean half-life in rabbits is 44 minutes while in humans the mean half-life of absorbed glycine was 173 minutes (own observations). The presented animal data demonstrate the glycine levels at 10, 20, 30 and 40min to be comparable with those found at the end of the intervention in several patients subjected to TURP. Indeed, several of our patients had plasma glycine levels of 10mM and in one patient levels up to 16.6mM were measured.

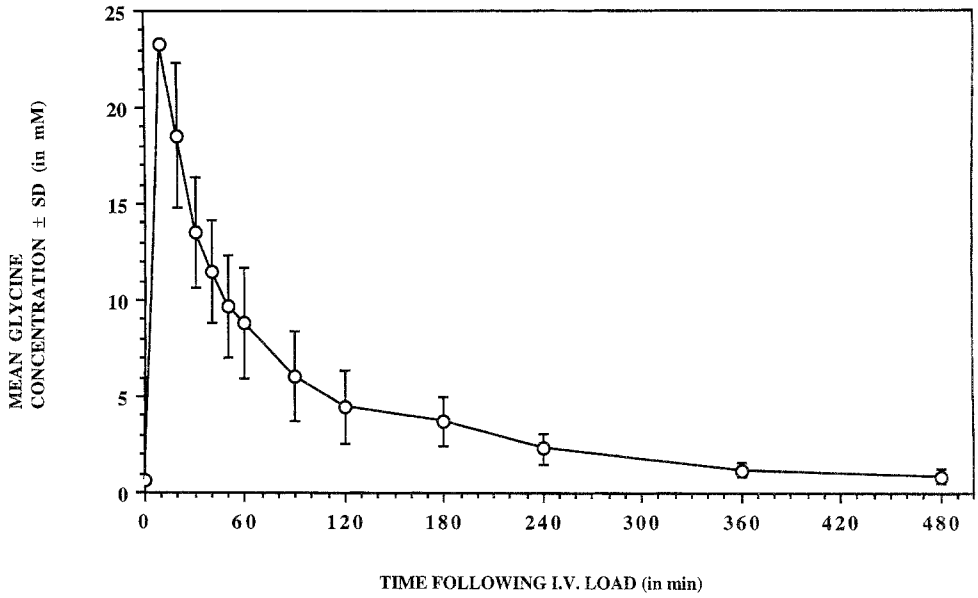

Fig. 1. Time-dependent plasma concentrations of glycine in rabbit following intravenous load

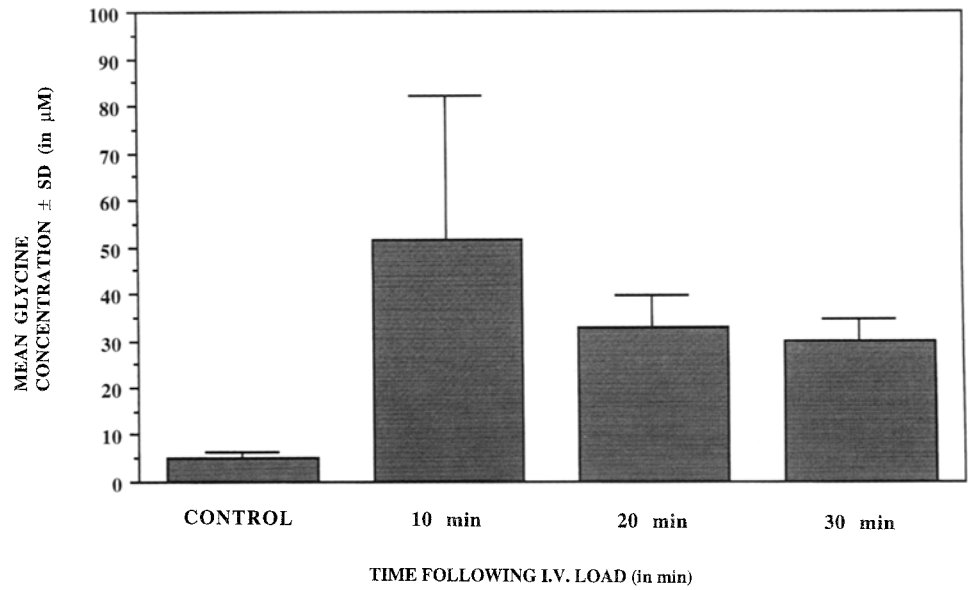

Fig. 2. Time-dependent cerebrospinal fluid concentrations of glycine in rabbit following intravenous load

Changes in glycine cerebrospinal fluid (CSF) concentrations in rabbit after intravenous glycine load

Figure 2 illustrates the time-dependent CSF concentrations of glycine in rabbits following a 10 mmol/kg intravenous administration of glycine. CSF levels of glycine rose approximately tenfold from 5.02 ± 1.40 μM (n = 10) at time 0 to 51.5 ± 30.5 μM (n = 10) at ten minutes (n = 5). Consequently, CSF glycine

levels time-dependently decreased to 32.8 ± 6.60μM (n = 7) and 29.6 ± 5.0μM (n = 7) at respectively 20 and 30 minutes after intravenous glycine load.

Increases of glycine content in different regions of the central nervous system (CNS) of experimental animals following glycine load

Glycine concentrations in different CNS regions of non-challenged rabbits ranged widely from 0.925 ± 0.228μmol/g wet weight in cerebellum to 2.53 ± 0.594μmol/g wet weight in medulla oblongata (Table 1). At 10 and 30min after glycine load, glycine was found to increase in all considered regions. Increases of glycine levels ranging from 14% (in mesencephalon) to 93% (in hypothalamus) were observed after 10 minutes while increases ranging from 27% (in pons) to 100% (in hippocampus and frontal cortex) were found after 30 minutes. All increases were found to be statistically significant except in medulla oblongata, pons and mesencephalon after 10min.

Increase of glycine concentrations in ocular structures following intravenous glycine load

Glycine concentrations were determined in anterior chamber fluid, vitreous humor and retino-choroid tissue in non-challenged animals and at 10 and 30min after i.v. glycine load (10mmol/kg). After i.v. glycine load, glycine levels increased significantly in all studied samples at all considered times (Table 2). In retina-choroid and vitreous humor, increases were highest at 10 minutes (respectively five- and tenfold) while increases in anterior chamber fluid were approximately tenfold at 10 minutes and about thirteenfold at 30 minutes.

Table 1. Glycine concentration (in μmol/g tissue) in different regions in rabbit brain following i.v. load

	Control (n = 8)	10min (n = 4)	30min (n = 6)
frontal cortex	1.01 ± 0.24	1.47 ± 0.16*	2.03 ± 0.31**
occipital cortex	0.99 ± 0.14	1.58 ± 0.45**	1.80 ± 0.28***
cerebellum	0.92 ± 0.23	1.36 ± 0.14*	1.80 ± 0.50***
striatum	1.03 ± 0.21	1.28 ± 0.09*	1.59 ± 0.25**
hippocampus	0.97 ± 0.20	1.27 ± 0.28*	1.95 ± 0.43***
thalamus	1.28 ± 0.09	1.58 ± 0.21**	1.81 ± 0.16***
hypothalamus	1.51 ± 0.31	2.90 ± 1.25*	2.88 ± 0.47*
mesencephalon	1.47 ± 0.26	1.68 ± 0.23^{NS}	2.33 ± 0.38**
pons	2.47 ± 0.27	3.23 ± 0.94^{NS}	3.13 ± 0.45*
medulla oblongata	2.53 ± 0.59	3.61 ± 0.62^{NS}	3.79 ± 0.46**
spinal cord	1.59 ± 0.32	2.42 ± 0.36**	3.05 ± 0.63***

Results are expressed as mean ± standard deviation. Significance of differences between the control and the experimental values was determined using Mann-Whitney U test. * = $p < 0.05$, ** = $p < 0.01$, *** = $p < 0.001$, *NS* not significant.

Table 2. Glycine concentration in rabbit eye following i.v. load

	Control (n = 9–10)	10 min (n = 8)	30 min (n = 6)
Retina-Choroid (in μmol/g)	0.90 ± 0.20	4.90 ± 1.50***	3.63 ± 1.15**
Vitreous Humor (in μM)	0.025 ± 0.004	0.24 ± 0.08***	0.20 ± 0.04**
Aqueous Humor (in μM)	0.42 ± 0.08	3.94 ± 1.41***	5.58 ± 1.66**

Results are expressed as mean ± standard deviation. Significance of differences between control and experimental values was determined using Mann-Whitney U test. * = $p < 0.05$, ** = $p < 0.01$, *** = $p < 0.001$.

Discussion

The aim of the animal model was to simulate hyperglycinemia associated to TURP and to use the model to study alterations in glycine content of brain and ocular tissues. The importance of this investigation is related to the neurotransmitter function of the studied amino acid. More specifically, we are interested in the involvement of transient hyperglycinemia in two complications of TURP: TURP syndrome and visual disturbances. Different hypotheses for the pathogenesis of TURP syndrome have been proposed but the possible implication of hyperglycinemia in the pathophysiology of this complication has not been investigated.

Plasma glycine levels in animals, receiving 10 mmol/kg glycine, remained above 10 mM, for approximately 40 minutes. Of interest is the concomitant rise of glycine concentration in CSF. This means that the active transport mechanism of excess glycine out of the CSF compartment is surpassed and unable to keep glycine in CSF at a low, normal level. The second point is that the temporary hyperglycinemia caused significant rise of the glycine content in different cerebral structures and in the retina and ocular fluids. It is likely that also in TURP patients similar changes in brain tissue and ocular structures occur. Permanent excess of glycine as observed in non-ketotic hyperglycinemia could contribute to the disastrous consequences for patients suffering from this metabolic disorder. Transient hyperglycinemia however, might be involved in temporary blindness following transurethral prostatectomy.

Based on a clinical study, Mizutani et al. (1990) suggested a link between high serum glycine concentrations and visual disturbances. However, the authors did not find a distinct serum glycine threshold with respect to the visual symptomatology, nor did they find a correlation between the severity of visual defect and the degree of hyperglycinemia. Experimental evidence for the influence of hyperglycinemia on vision was published by Wang et al. (1989). These authors investigated alterations of visual evoked potentials (VEPs) in dogs receiving glycine intravenously. In all experimental animals, the VEPs were distinctly altered: peak latencies of "P50" increased and the amplitudes of "N100" were reduced (P50 = prominent positive component after +/− 50 milliseconds; N100 = amplitude of the largest negative wave peaking at around 100 milliseconds). Although serum concentrations of

glycine and ammonia were both significantly elevated the authors favored glycine as the offending substance rather than ammonia.

Some authors (Appelt et al., 1979; Cashman, 1990; Russell, 1990) suggested occipital cerebral edema – due to hyponatremia – as the etiology for transient blindness. However, in cortical blindness, light perception is completely lost, which is not the case in TURP associated visual problems. The presence of glycine in a large number of retinal neurons has been confirmed by autoradiographic and immunocytochemical studies (Frederick et al., 1984; Marc et al., 1985; Hendrickson et al., 1988).

Sufficient data seems to be available to consider glycine (and GABA) as an inhibitory transmitter in the retina known to have a strychnine-sensitive glycine receptor (Kirby, 1979; Belgum et al., 1984). But there is increasing evidence that glycine may also serve as a modulator at excitatory N-methyl-D-aspartate (NMDA) receptors in retina (Pourcho et al., 1990). Our investigations seem to confirm the conclusions of Mizutani et al. (1990) and Wang et al. (1989). Mizutani et al. found elevated glycine and high ammonia concentrations in their patients but asymptomatic patients displayed a greater increase in serum ammonia compared to patients with visual problems. Wang and coworkers found also high glycine and ammonia levels in experimental dogs. However, glycine levels decreased rapidly over time and this decrease was associated with improvements of the altered VEP waves while ammonia levels still remained high. For these reasons, both authors favor glycine rather than ammonia as the offending substance. The observed rapid increase in glycine content in ocular structures may disturb the neuronal circuitry in the retina. How glycine influences vision is not clear to date because the neuronal circuitry in the retina is complex and opposite activity of this neurotransmitter is possible.

Whether or not glycine is involved in the cardiovascular and neurological disturbances seen in TURP syndrome is not evident. Different etiologic mechanism have been proposed to explain this complication: dilutional hyponatremia, ammonia intoxication and volumetric overload. Dilutional hyponatremia does occur in 7 to 20% of TURP patients (Rhymer et al., 1985; Henderson et al., 1980; Ghanem et al., 1990) and causes cerebral edema which in turn produces an increase in intracerebral pressure. Increased intracerebral pressure can explain hypertension, bradycardia, agitation, convulsions and coma. Most clinical reactions occur when serum sodium drops 15 to 20 mEq/l below the normal value of 135 mEq/l (Henderson et al., 1980). Confusing is the fact that some patients with low serum sodium levels (98 to 125 mEq/l) in the study of Henderson et al. (1980) experienced only mild symptoms. Moreover, the characteristic combination of hypotension and bradycardia as seen in TURP syndrome, is not sufficiently explained. Since the publication of Hoekstra et al. (1983) hyperammonemia, the consequence of glycine metabolization, is regarded as a contributing factor or even as the origin of the encephalopathy in TURP syndrome (Ryder et al., 1984; Shepard et al., 1987). However, this complication may also develop in the absence of significant hyperammonemia (Hamilton Stewart et al., 1989). Recently, Ghanem et al. (1990) indicated volumetric overload and decrease in serum

osmolality as the main factors leading to TURP syndrome but the mechanism by which hypervolemia induces hypotension and shock remains the most obscure aspect of this explanation.

The lack of clarity about the etiology of TURP syndrome is an impulse to further explore the influence of transient hyperglycinemia. Indirectly, the ammonia production after glycine absorption may contribute to the encephalopathy of TURP syndrome. However, direct influence of the glycine excess in brain tissue in the symptomatology of TURP syndrome is not established. Theoretically, high glycine content in the perineural space could generate neurogenic side effects due to its complex neurotransmitter function. Moreover, experimental data suggest that glycine may be implicated in cardiovascular control in rats (Kubo et al., 1987). Microinjection of glycine (and GABA) delivered in the area of the nucleus tractus solitarius produced a dose dependent increase in blood pressure and an increase in heart rate. Recently, Schmid and coworkers (1991) provided evidence for strychnine sensitive glycine receptors to play an important role within the respiratory system. These authors injected glycine in the fourth ventricle of rabbits. Glycine increased the time of expiration and to a lesser extend also the time of inspiration. Glycine injected in higher doses (250μg) reduced the phrenic nerve activity in the experimental animals.

In conclusion, the mechanisms responsible for transient blindness and TURP syndrome following endoscopic prostatectomy are not defined. Our experimental observations indicate that the prerequisites for possible neurogenic side effects are present in transient hyperglycinemia associated with TURP. Further exploration of the pathophysiology of postoperative hyperglycinemia is mandatory to find the missing answers. We propose our model as an experimental tool for researchers interested in unraveling the pathophysiology of this most intriguing syndrome.

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Authors' address: Prof. Dr. B. Marescau, Department of Medicine-UIA, Laboratory of Neurochemistry and Behavior-BBS, UIA, T 504, Universiteitsplein 1, B-2610 Antwerp, Belgium.

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