Biological Availability of Endogenous Calcitonin in Rats

R. A. Krasnoperov

Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 125, No. 4, pp. 474-476, April, 1998
Original article submitted February 19, 1997

Significant correlation was established in 52-week-old rats between serum calcitonin content and density of sublemmal granules at the vascular pole of C-cells (N_{Vsg}): r_{xy}=0.922, p<0.001. Statistical simulation methods made it possible to determine the confidence interval of biological availability of endogenous calcitonin: 87-100% (p≥0.95).

Key Words: *thyroid C-cells; biokinetics; statistical simulation; transmission electron microscopy*

Phenomenological and ultrastructural parameters of the blood-C-cell (BCC) barrier formed in the adjacent zone of thyroid C-cell and perifollicular capillary were described earlier [2]. Due to its boundary location, the BCC system can determine the probability of calcitonin (CT) supply to vascular bed, i.e., to control biological availability of endogenous calcitonin (F_{CT}). However, regulating activity of the BCC complex has not been investigated, mainly due to lack of data on CT kinetics in the region of BCC interaction. The first step in this direction is made in this work, aimed at evaluation of F_{CT} in normal rats of reproductive age.

MATERIALS AND METHODS

The study was carried out on 18 male albino rats at the age of 52 weeks. Serum CT was determined by radioimmune assay (RIA) with a RIA-mat Calcitonin II kit (Mallinckrodt Diagnostica). The intraseries variation coefficient CV_{RIA} was 7.34% (n=30). The thyroid material was prepared for electron microscopy by the standard methods. Visual analysis and photography of the preparations were performed in a JEM-100B electron microscope. The formal boundaries of BCC interaction zone under morphometric study were determined as previously [1]. Evaluation of incretory activity of thyroid perifollicular epithelium was performed according to N_{Vsg} [3]. BCC transport of CT into system is blood flow was approximated by the process of intercompartment mass transfer using an open two-chamber model, in which the first chamber represents the sublemmal cytoplasmatic compartment of the vascular pole of C-cell and the second chamber represents systemic blood flow.

Research Center of I. M. Sechenov Medical Academy, Moscow

RESULTS

The correlation analysis detected a significant statistical relationship between the intensity of transfer of secretory granules from a C-cell (X) and serum CT content (Y): r_{xy}=0.925 (p<0.001). Transformation of the regression model Y=a+bX into the covariant one (Y=bX) is characterized by a close to unity covariation coefficient (r_{xy}=0.99916; p<0.0001) and negligible of prognostic error (a residue σ_{res}=4.11%). This attests to essential predetermination of serum concentrations CT(Y) by incretory activity of thyroid perifollicular epithelium (N_{Vsg}).

At the same time, the resulting parameter (Y) depends not only on the corresponding predictor variable (N_{Vsg}), but also on a number of factors that are not accounted in the model (such as delay of CT at the transinterstitial and/or transmural stages of BCC transport). The number of factors that increase the residue of covariant prognosis for the discussed statistical relationship is infinitely great. Therefore,

0007-4888/98/0004-0420$20.00

there may be only an approximate answer to the question what fraction of the root-mean-square deviation of the prognostic error of Y via X is caused by losses of CT during mass transfer between compartments of the BCC barrier. It is obtained by subtraction of the dispersion caused by the factors of known potency to aggravate the statistical prognosis (one of such factors is the instrumental error of radioimmunological assay) from the total dispersion of the covariant model. Thus,

$$\sigma^2_{BCCD}=\sigma^2_{res}-CV^2_{RIA}-\sigma^2_{extr}, \text{ or}$$
$$\sigma^2_{BCCD}<\sigma^2_{res}-CV^2_{RIA}, \quad (1)$$

where σ_{BCCD} is the mean square deviation of covariant prognostic residue caused by BCC-delay of CT, CV_{RIA} is the coefficient of intraseries variation of the RIA kits, σ_{extr} describes the effect of some extraneous nonaccountable factors. The solution of inequality (1) is $\sigma_{BCCD}<1.45\%$ with prognostic probability $p>0.95$, which was obtained for the following conditions: $\sigma_{res}=4.11\%$ (n=18), confidence interval 2.51% ($p=0.05$) — 6.71% ($p=0.95$) and $CV_{RIA}=7.34\%$ ($n=30$), confidence interval 5.38% ($p=0.05$) — 10.01% ($p=0.95$).

The variation coefficient is the mean square deviation is expressed in the fractions of the mean value: $CV=\sigma/X$. Thus, $\sigma=CV\times X$. If X corresponds to BCC-delay of CT (to be denoted by L, %), for the considered problem $CV_L\times L$ *is* equal to the mean square deviation of CT delay. Therefore, the ratio $CV_L\times L$ to $100-L$ is the mean square deviation of BCC-losses of CT expressed in fractions of part of hormone, that is secreted into systemic blood flow. In other words, the ratio $CV_L\times L$ to $100-L$ is variation of the available fraction of endogenous CT caused by hormonal losses during the BCC mass transfer between the compartments. Hence, $L=100-F_{CT}$ (%) or $\sigma_{BCCD}=CV_L\times L/(100-L)$. This equation yields

$$L=100\times\sigma_{BCCD}/CV_L+\sigma_{BCCD} \quad (2).$$

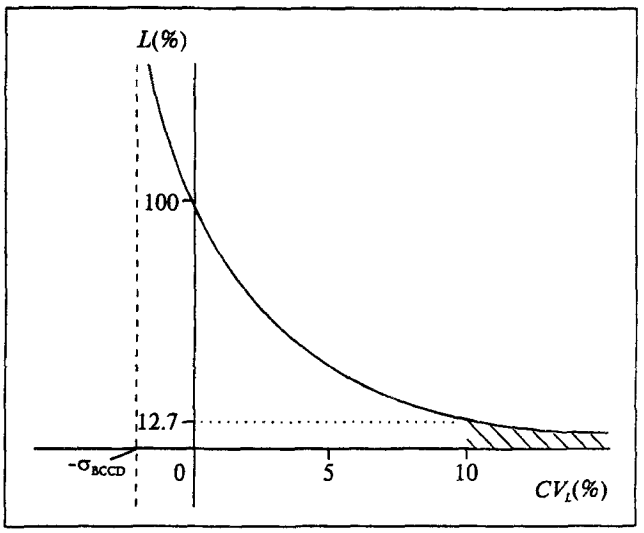

Fig. 1. Dependence of BCC loss of CT (L) on its variation coefficient CV_L is illustrated by an equilateral hyperbola with the asymptotes $CV_L=\sigma_{BCCD}$ and $L=0$. The function assumes a biological interpretation at nonnegative values of the argument: with increase in CV_L the degree of BCC-delay of CT in the thyroid drops monotonousey from 100 to 0%. Hatched area corresponds to the admission that $CV_L\geq 10\%$.

The dependence of BCC delay of CT on CV_L is illustrated by hyperbola (Fig. 1). Estimation of maximum level of the intrathyroid losses of CT(L) is made with admission on minimal CV_L value (i.e., the variation coefficient of BCC-delay of CT in the examined group of rats). Table 1 shows the data on variability of pharmacokinetic parameters of exogenous CT. Taking into account the residual coefficient of variation, which is not smaller than 12% in all the cases given in Table 1, we assume that

TABLE 1. Literature Data on Variation of Some Parameters of Pharmacokinetics of Exogenous CT

Parameter	CV_1, %	CV_2, %	CV_3, %	Reference
Half-distribution period ($t_{1/2\alpha}$) by intravenous administration of CT	18.2	<10.7	>14.7	[4]
Half-elimination period ($t_{1/2\beta}$) by intravenous administration of CT	17.5	<10.7	>13.8	[4]
Area under the time-concentration curve (*AUC*) by intravenous administration of CT	16.1	<10.7	>12.0	[4]
AUC by intravenous administration of CT	40.3	14.3	37.7	[5]
Stoichiometric coefficient α of exogenous CT	18.3	10.0	15.3	[6]
Stoichiometric coefficient β of exogenous CT	32.7	10.0	31.1	[6]
Volume of distribution of exogenous CT	19.1	10.0	16.3	[6]

Note. The residual variation coefficient (CV_3) was calculated from the formula $\sqrt{CV_3^2=CV_1^2-CV_2^2}$, where CV_1 is the variation coefficient of the pharmacokinetic index, CV_2 the interseries variation coefficient of the kits that were used to determine serum CT. The true measurement error of the table data is less than CV_2, because approximation of the concentration-time curves (for example, numerical integration by estimation of *AUC*) is characterized by a decrease in the measurement error of the secondary index [8].

BCC-delay of CT in rat thyroid gland varies by no less than 10% of the mean value, i.e., $CV_L \geq 10\%$. The solution of equation (2) under the given conditions is $L<13\%$ (prognostic probability $p \geq 0.95$). Consequently, $F_{CT}>87\%$ ($F_{CT}=100-L$).

The obtained estimate of F_{CT} makes it possible to conclude on the absence of significant losses of CT at the stages of BCC mass transfer in the normal rat thyroid. Presumably, CT molecules cross the BCC barrier in the form of relatively directed flow with nonsignificant intrathyroid distribution. Utilization of the hormone by the structures in volved in the BCC interaction seems to be negligible. The latter inference agrees with the fact that the density of CT receptors in the thyroid is not high [7].

REFERENCES

1. R. A. Krasnoperov, S. V. Gratchev, V. A. Glumova, *et al.*, *Arkh. Patol.*, **58**, No. 1, 68-70 (1996).
2. R. A. Krasnoperov, S. V. Gratchev, V. A. Glumova, *et al.*, *Ontogenez*, **27**, No. 2, 131-136 (1996).
3. R. A. Krasnoperov, S. V. Gratchev, V. A. Glumova, *et al.*, *Tsitologiya*, **38**, No. 4-5, 560-563 (1996).
4. K. H. Antonin, V. Saano, P. Bieck, *et al.*, *Clin. Sci.*, **83**, No. 5, 627-631 (1992).
5. K. Overgaard, D. Agnusdei, M. A. Hansen, *et al.*, *J. Clin. Endocrinol. Metab.*, **72**, No. 2, 344-349 (1991).
6. B. L. Riggs., C. D. Arnaud., R. S. Goldsmith, *et al.*, *Ibid*, **33**, No. 1, 115-127 (1971).
7. P. M. Sexton, H.-G. Schneider, C. S. Santos, *et al.*, *Biochem. J.*, **273**, No. 1, 179-184 (1991).
8. O. C. Zienkiewicz and K. Morgan, *Finite Elements and Approximation, New York* (1983).