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ENDOGENOUS BETA-ADRENERGIC RECEPTOR ANTAGONISTS (EBARA) IN HEALTH AND DISEASE

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Data accumulated in investigations under in vivo and in vitro conditions confirm author's concept about the existence of EBARA, certain endogenous biologically active substances in a healthy and pathologically altered organism when no beta-adrenergic blockers of synthetic, semi-synthetic, and natural origin have been introduced. Based on the suggested model about the interrelation between the endogenous specific beta-adrenergic receptor antagonists (ESBARA) and the endogenous non-specific beta-adrenergic receptor antagonists (ENBARA) it has been accepted that "three of four agonist-activated G-protein-coupled beta-adrenoreceptors" are under the antagonistic control of beta-arrestins (specific co-factors of 6 izoenzyme beta-adrenoreceptor kinases) through their phosphorylation (Lefkowitz' group) while the fourth beta-adrenoreceptor is, probably, antagonized by urea, manganese ions, hydrogen peroxide, L-taurine, etc. The efforts of the groups of Lohse and Di Blasi demonstrated a superexpression of beta-arrestins in patients with heart failure when no other reason was present at all. Data about ENBARA indicate their involvement in patients with chronic renal failure on periodic haemodialysis and with cystic kidney fibrosis as well.

Key-words: EBARA, ENBARA, ESBARA, urea, isoproterenol, arrestin, renal failure

Until recently, the problem of endogenous beta-adrenergic receptor antagonists (EBARA) has not been discussed in the biomedical and clinical literature (10-12). Based on own results obtained under in vivo and in vitro conditions, our group describes "urea as endogenous metabolic factor with behaviour of a non-selective beta-adrenergic receptor blocking agent" (8). It is to be underlined that using scattered literature data we develop a concept of endogenous non-specific beta-adrenergic receptor antagonists (ENBARA) and of endogenous specific beta-adrenergic receptor antagonists (ESBARA) (10-12). Further developing our concept of ENBARA and ESBARA we accept that under physiological conditions both EBARAs act as endocoids (autacoids), i. e., our drugs of organism in agreement with Lal et al. (1984, cited after 11). It is possible that in early disorders of homeostasis and under pathophysi-

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ologic conditions both EBARAs are enlarged, too (1,9,11,13).

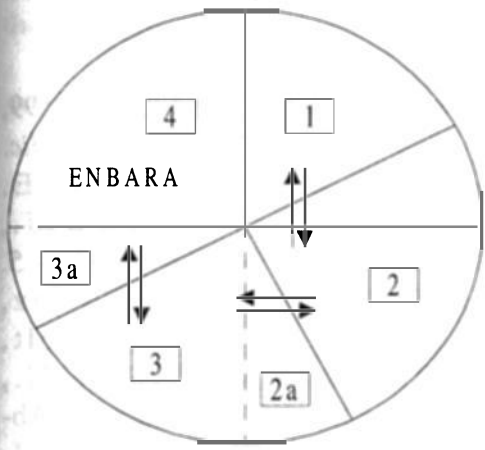
Data under in vivo conditions supporting the concept of ENBARA originate from experiments carried out on anaeshetized cats and dogs (11) and rats (7). Results show that: 1) isoproterenol (+)-chronotropic and vasodepressor effects ranging 1-2-4 nmol i. v., prior to and at 1st, 2nd, 3rd, 4th and 5th h after single injection of urea 17 nmol/kg i. v. are dose- and time-dependently antagonized to significant degree and 2) after repeated infusions of isoproterenol the vasodepressor responses were completely inhibited but the positive chronotropic effects were partially inhibited after manganese infusion (1 mg/kg/min $MnCl_2$). However, Strubelt's team concluded that "manganese is not a beta-blocking substance. If this were so, calorigenic and positive chronotopic action would be equally inhibited" (8). German pharmacologists believed that the principal criterion was the adequacy between cardiovascular and metabolic effects of beta-adrenoblockers and manganese ions in parallel.

Data under in vitro conditions supporting the concept of ENBARA also originate from several groups of investigators. We could demonstrate a non-specific, non-selective, and non-competitive antagonism of isoproterenol and fenoterol relaxation in arterial and venous preparations at isotonic and isometric regimens (12). Urea 10-100 mM decreased noradrenaline contractile effects and mechanical activity of guinea-pig isolated heart - a beta-1,2-adrenergic response (Kersing and Brass, 1976, cited after 11). Similar data about manganese ions were obtained showing positive inotropic effect of adrenaline in guinea-pig atria (Meinertz and Scholz, 1969, cited after 11). The antagonistic effects of hydrogen peroxide on beta-adrenoceptors such as inhibition of adenylyl cyclase activity and cAMP content in calf heart membrane preparations were described (2). The antagonistic effect of L-taurine on isoproterenol inotropism of chick heart was reported (5).

Data under clinical conditions supporting the concept of ENBARA originate from our clinico-pharmacological approach as a logic continuation of experimental pharmacological data with urea as ENBARA. We studied haemodialyzed and healthy males. Using a time-plateau concentration principle we performed an isoproterenol infusion of 12-24-48-96 pmol/kg/min immediately before and after the end of 4th hour of regular haemodialysis procedure. In contrast to the control age-matched group we observed an absent dose-response curves fashion of isoproterenol (+)-chronotropic and vasodepressor effects before the haemodialysis procedure. Removal of urea by 55 % at the end of the same procedure was the major factor for significantly restored isoproterenol (+)-chronotropic effect (9). Decreased cardiac beta-adrenoceptor responsiveness was reported in patients with cystic fibrosis (Motulsky and Insel, 1982, cited after 11) and attributed to chronic renal failure.

Data under in vitro conditions supporting the concept of ESBARA_appeared since 1990 up to now. Lefkowitz's group isolated beta-arrestin, a 418-aminoacid protein homologous to the retinal arrestin regulating beta-adrenergic receptor function of 75 % agonist-activated beta-adrenoceptors (4). Beta-arrestin-2, a novel member of the arrestin-beta-arrestin-gene family exhibited 78 % aminoacid density with beta-arrestin-1. They acted as specific co-factors of beta-adrenergic-receptor kinases 1 and 2. Both beta-arrestins were equipotent and predominantly localized in neuronal tissues exerting homologous desensitization of beta-adrenergic receptors.

Data under clinical conditions supporting the concept of ESBARA started since 1994 and continue up-to-date.

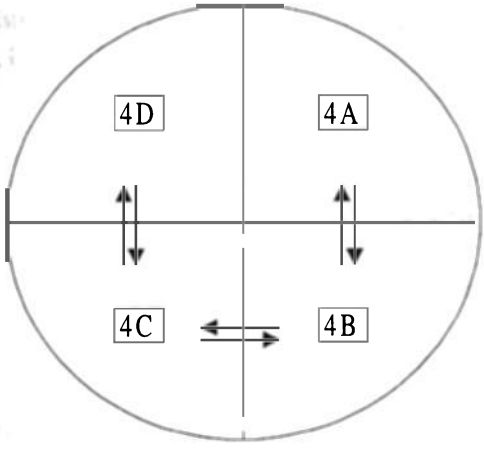


ESBARA

ESBARA

1 - beta-arrestin 1
2 - beta-arrestin 2
3 - arrestin 3
1, 2, 3 - co-factors of 6 ßARK
(ß-Adrenergic Receptor Kinases)

ß-ADRENERGIC RECEPTOR - MEDIATED ENDOCYTOSIS - INDUCED DOWN REGULATION
(Schematically presented by 1a, 2a, 3a)



ENBARA

ENBARA

A - carbamide (urea)
B - manganese ions ($MnCl_2$)
C - hydrogen peroxide
D - l-taurine

Fig. 1. *Schematic presentation of ESBARA and ENBARA modelling in vertebrates*

United efforts of German pharmacologists and clinicians revealed an expression of beta-arrestin and beta-adrenergic receptor kinases in the failing human heart (13). Benovic's group found out an increase in beta-adrenergic receptor kinase 1 protein expression from younger hypertensive patients (1).

This enzyme activity increase probably underlies the reduced beta-adrenergic receptor responsiveness typical of the hypertensive state (11,13).

In conclusion a lot of data, own and from the recent literature available, undoubtedly support the role of EBARA under physiological and pathological conditions in animals and humans. Schematically, our model was presented in Fig. 1 reflecting ENBARA and ESBARA interrelationships.

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Ендогенните бета-адренергични рецепторни блокери (ЕБАРА) при здраве и при болест

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Резюме: Натрупаните до сега данни за изследвания в условия *in vivo* и *in vitro* поддържат развиваната от автора концепция за ЕБАРА - определени ендогенни биологично активни вещества в здравия и в болния организъм, когато не са въвеждани

бета-адренергични блокери от синтетичен, полусинтетичен или природен произход. На базата на предложения модел за съотношението на ендогенните специфични бета-адренергични рецепторни блокери (ЕСБАРА) и ендогенните неспецифични бета-адренергични рецепторни блокери (ЕНБАРА) се приема, че "три от четири агонист-активирани G-протеин-куплирани бета-адренорецептори" са под антагонистичния контрол на бета-арестини (специфични ко-фактори на 6 изоензима бета-адренорецепторни кинази) чрез тяхното фосфорилиране (групата на Lefkowitz), а четвъртият бета-адренорецептор вероятно се антагонизира от урея, манганови йони, водореден прекис, L-таурин и др. Усилията на групите на Lohse и Di Blasi показаха суперекспресия на бета-арестини при болни със сърдечна недостатъчност, без да има друга причина. Данните за ЕНБАРА сочат участието им при болни с хронична бъбречна недостатъчност на периодична хемодиализа и с цистична фиброза на бъбреците.