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ON THE ISSUE OF BIOLOGICAL RECEPTORS: FUNDAMENTAL DATA THAT HAVE BEEN FORGOTTEN OR NEGLECTED

Aim. The biological action of chemical and physical factors can be carried out in three stages: (1) stimulation, (2) inhibition and (3) collapse of chemical reactions. Externally, these reactions manifest themselves as stimulation or inhibition of physiological (growth) processes or death of the biological object. There are still no convincing data on how these processes are regulated at the molecular level. Experimantal data on why some substances are biologically active while others are not in comparable doses are also absent. The structure of molecules that determine their biological activity has not been identified either. The aim of the study was to identify the specific structure of molecules that determine their biological activity based on the analysis of the steric structure of various chemical compounds. ***Results***. After analyzing the structure of various biologically active substances (toxins, agricultural and pharmaceutical chemicals), the active hydrogen atom was identified at the N- or C-atoms in the bilateral environment by electron-withdrawing groups, as well as the presence of unsaturated bonds in aliphatic or cyclic structures, but not in aromatic cycles. ***Conclusions***. It is concluded that such fragments of molecules determine the biological activity of chemical compounds.

Keywords: BACs, Structure-Activity Relationships, receptors.

The biological action of chemical and physical factors can be carried out in three fixed stages: (1) stimulation, (2) inhibition and (3) collapse of chemical reactions. Experimantal data on why some substances are biologically active while others are not in comparable doses are absent. The structure of molecules that determine their biological activity has not been identified either. There are still no convincing data on how these processes are regulated at the molecular level. There is no information on how physical factors can cause reactions in the living system similar to chemical substances. It was suggested that the interaction of chemical agents with the genome of the biological cell are carried out by original mediators of the protein nature. Cross-talk bioregulators interaction later cast doubt on this idea, since the number of natural and synthetic bioregulators is many times greater than the number of mobile proteins in the biological cells. This paper does not consider the molecular mechanisms of action of biologically active compounds (BACs). Here I review the prehistoric data of the protein receptor theory that have been forgotten or neglected.

1. Starting point for a theory of biological receptors

The toxic effect of chemical agents on biota has long been known. Paracelsus also noted: «What is there that is not a poison? All things are poison, and nothing is without poison. Solely the dose determines that a thing is not a poison». Today, the term poison is used as BACs. But the conflict lies in the fact that in relatively equal doses, some substances act as poisons, while others do not. This was the reason for research such phenomenon. The synthesis of radioactive substances contributed to establish their localization sites in tissues and cells.

Studies in the 70–80 years unambiguously established the localization of labelled BACs in the membranes of various plant and animal cells (Table 1).

The histological data from these studies showed localization of the labeled substances predominantly on the plasmalemma and to a lesser extent on intracellular membranes. Given the large amount of similar data, there is therefore no need to continue this table. Thus, these studies became the logical starting point in the search for the causes of the biological activity of chemical compounds.

The second important conclusion of this period was established fact of changes in the physiccochemical properties of membrane structures.

Table 1. Localization of labelled BACs in membranes of various plant and animal cells

Labelled chemicals	**Membranes from the tissues**	**Publications**	
1-naphthylacetic acid ([^{14}C]NAA)	Coleoptiles of *Zea mays* L., cv Kelvedon 33L., cv Kelvedon 3	[1]	
Dihydrofusicoccin [^{3}H]FC	Oat root tissue of *Avena sativa* L. cv. Victory	[2]	
Gibberellic acid, (a GA_4/GA, mixture)	Phospholipid membranes	[3]	
N-1-aphthylphthalamic acid [^{3}H]NPA	Corn (*Zea mays* L.) seedlings	[4]	
^{35}S-labelled formylmethionyl methyl phosphate	Red blood cell	[5]	
Saxitoxin	Rabbit vagus nerves	[6]	
α-Bungarotoxin	*Torpedo marmorata*	[7]	
^{75}Se-labelled human parathyroid hormone ^{125}I- labelled human parathyroid hormone	Bovine kidneys	[8]	
^{131}I	Semen of white boars	[9]	
^{125}I-labelled human follicle-stimulating hormone	Bovine testes	[10]	
Chlorpromazine	Erythrocyte ghosts	[11]	
Phorbol-12-13-dibutirate (^{3}H-PDBu)	Mink lung cells	[12]	

The localization of radioactively labeled substances, primarily on the plasmalemma, and the simultaneous changes in the physicochemical properties of membranes and their physiological functions led to the conclusion that the initial mechanism of bioregulator actions is connected with membrane structures.

2. Fundamental data that were missing or ignored

The discovery that labeled BACs were associated with the plasmalemma led to the idea that this was related to their biological activity. It was assumed that the steric structure of BACs (as a kind of key) should correspond to the relief area on the outer side of the plasmalemma.

Also, it was assumed that such complex should lead to changes in the structure and function of the plasmalemma. Therefore, some signal (called as a receptor) must emanate from the membrane into the cytoplasm and initiate transcription.

Given the large amount of literature, I do not quote such data selectively. Moreover, no patterns were found. The reason was the difference in the structural sizes of BACs from small nitric oxide and ethylene to large peptide structures.

Therefore, the next stage of research was the study of the steric structure of BACs. Particular attention has been focused on the presence of halogens in BACs.

Experimental data indicated a sharp increase in the biological activity of fluorinated and chlorinated substances. Although such research continues to this day, the reason why some substances are chemically and biologically active and others are not has not been clarified.

Approaches such as combinatorial chemistry and computer-based molecular modeling design did not turn out to be revolutionary. Although the libraries contain thousands of substances, the synthesis of new BACs continues at random.

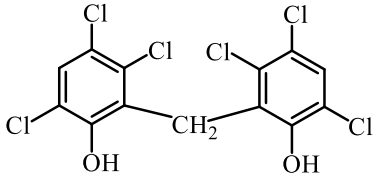
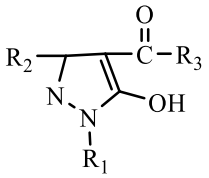
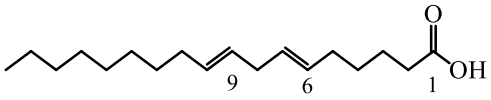
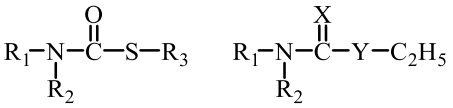
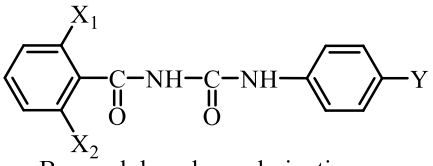
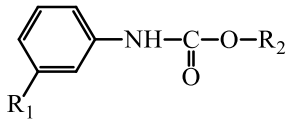
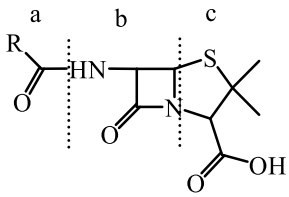
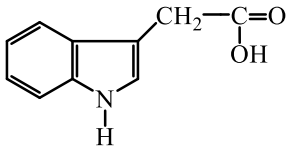
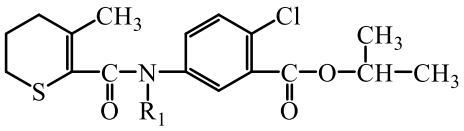
After analyzing the structure of various biologically active substances (toxins, agricultural and pharmaceutical chemicals), was determined the active hydrogen atom at the N- or C-atoms to be in the bilateral environment by electron-withdrawing groups, as well as the presence of unsaturated bonds in aliphatic or cyclic structures, but not in aromatic cycles [13–15], as shown in Table 2.

Thus, all bioregulators considered above, are characterized by the obligatory presence of active hydrogen atom or double bonds. Unfortunately, these fundamental data were forgotten or ignored by researchers when defining proteins as receptors.

3. Protein receptors. More questions than answers

This publication does not consider the theory of protein receptors. The article offered to readers contains the author's personal point of view on this problem. It presents data preceding the formation of the theory of reception, in particular protein receptors. Attention is drawn to the fact that when considering protein receptors, the steric structure of biologically active compounds is not taken into account. But only substances of the strictly defined structure can exhibit the biological effect. Even in the presence of receptor proteins, many compounds are biologically inert. Due to the overly complicated mechanisms of the receptor theory, many questions arise for which there is no convincing experimental data.

Table 2. Chemistry and Structure–Activity Relationships of diverse BACs

The anti-tuberculosis drug hexachlorophene possesses in strong antibacterial effect only when there is a methylene bridge at the 2,2' position [16].	 Hexachlorophene
Herbicidal activity of 4-acylpyrazole derivatives were the most active in the presence of the hydrogen atom at R_1 [17].	 4-acylpyrazole derivatives
Fatty acids possess in biological activity in the presence of unsaturated bonds [18, 19].	 Linoleic acid
The highest fungicidal activity among thiocarbamates was observed in compounds with R_1=H. [20].	 Thiocarbamates
The presence of the HN-group in benzoylphenylurea derivatives is mandatory for the manifestation of insecticidal activity [21].	 Benzoylphenylurea derivatives
The presence of the hydrogen atom at the nitrogen atom is necessary to inhibit the electron transport of photosystem II [22].	 Phenylcarbamates
In the structural formula of these antibiotics, three parts are distinguished: a) the side part, b) the β-lactam ring, and c) the thiazolidine ring. The presence of the β-lactam intact ring is essential for biological activity [23].	 *Beta*-lactam antibiotics
The presence, at least one hydrogen atom at the methylene bridge, is necessary condition for the manifestation of biological activity for indole-3-acetic acid [24].	 Indole-3-acetic acid
An anti-HIV agent is active if the R_1 radical is the hydrogen atom. When the hydrogen atom is replaced by a methyl group, the drug loses its activity [25].	

For example, how does formed the protein-bioregulator complex knows in which the chromosome is located the desired gene to proced transcription process?

How many proteins can serve as receptors to BACs? What is the nature of the chemical bond in this case? This is especially important for biologically active of protein BACs.

How many proteins are in membranes and how many of them are mobile, easily able to leave away from the membrane and combine with BACs?

Today, hundreds of thousands of natural and synthetic BACs are known (animal hormones, plant growth regulators, pesticides, drugs, terpenes, alkaloids, lipids, peptides, prostaglandins, etc.). Of these, plants have 150000–200000 bioactive natural chemicals and animals have 50000–100000 bioactive natural chemicals [26]. At the same time, human genome has about 20000 to 25000 protein-coding genes [27] and the Arabidopsis plant has also approximately 25000 protein-coding genes [28].

It is logical that there may be the insignificant proportion of mobile proteins to serve as receptors for such quantity of BACs. Hence, one protein, as a receptor, must «serve» several BACs. But then how can we explain in this case the selective action of plant growth regulators, pesticides, drugs, etc.?

In addition, there are evidence that sterically different BACs can initiate a similar biological effect [29]. Is the same receptor used in this case? But why, then, at high doses, the selective action of BACs is lost and becomes destructive, inhibitory or lethal? Are these actions realized through receptors?

Conclusions

This paper examined the relationship between the steric structure and the biological activity of various substances. Sterical structure of diverse BACs was considered in connection of their structure-activity relationships. It was discovered that the biological activity of chemicals is determined by presence of the active hydrogen atom at the N- or C-atoms in the bilateral environment of electron-withdrawing groups, as well as the presence of unsaturated bonds in aliphatic or cyclic structures, but not in aromatic cycles. Also, the fast or slow biological response depends on the N- or C-atom at which the active hydrogen atom is located.

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ДО ПИТАННЯ БІОЛОГІЧНИХ РЕЦЕПТОРІВ: ФУНДАМЕНТАЛЬНІ ДАНІ, ЯКІ БУЛО ЗАБУТО АБО ЗНЕХТУВАНО

Мета. Біологічна дія хімічних і фізичних факторів може здійснюватися в три стадії: (1) стимуляція, (2) гальмування і (3) зупинка хімічних реакцій. Зовні ці реакції проявляються у вигляді стимуляції або гальмування фізіологічних (ростових) процесів або загибелі біологічного об'єкта. Досі немає переконливих даних про те, як ці процеси регулюються на молекулярному рівні. Експериментальні дані про те, чому одні речовини біологічно активні, а інші ні в порівнянних дозах, також відсутні. Також не встановлено структуру молекул, що визначає їх біологічну активність. Метою дослідження на основі аналізу стеричної структури різних хімічних сполук було виявлення специфічної структури молекул, що визначає їх біологічну активність. ***Результати***. Після аналізу структури різних біологічно активних речовин (токсинів, сільськогосподарських і фармацевтичних хімікатів) ідентифіковано активний атом водню при N- і С-атомах в двосторонньому оточенні електроноакцепторних груп, а також наявність ненасичених зв'язків в аліфатичних або циклічних структурах, але не в ароматичних циклах. ***Висновки***. Зроблено висновок, що такі фрагменти молекул визначають біологічну активність хімічних сполук.

Ключові слова: БАР, структурно-активні зв'язки, рецептори.