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FOR AN INFORMATIONAL THEORY OF DOSAGE ILLUSTRATION FROM CELL AND MOLECULAR BIOLOGY AND PHARMACOLOGY

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INTRODUCTION

Understanding the role and importance of the cybernetic-informational mechanism of the pharmacodynamic action of drug (M), we argued for a cybernetic-informational pharmacology [1, 2, 13] that we developed in the last 10 years [3-14].

Thus, we :

- explained the informational mechanism of the pharmacodynamic action that we presented as cybernetic-informational phenomenon [10, 13];

- discussed the interference of M, considered as exogenous signal, with the active, endogenous, biological substances, considered as biological signals (S.B.), [3, 10, 13] and figured this M and S.B. interference at the level of both communication ways and cybernetic regulation mechanisms of the feed-before and feed-back type [3, 10];

- explained not only pharmacodynamics, but also pharmacotoxicology, from the cybernetic-information standpoint, considering M a polluting, disturbing element (P) and explaining the cybernetic-informational mechanisms of certain side effects of M [3, 10];

- discussed both informationally and cybernetically, the 4 adjustment modalities, i.e. izo-, homeo-, alo- and enantioregulation, through which homeopathic and allopathic drugs act [6, 11];

- emphasized the need to create a research methodology specific for cybernetic-informational pharmacology [5] and, consequently, we established two such original research methods [4, 7, 8, 9, 12];

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- demonstrated that information is a hidden parameter of the homeopathic drug, this idea being based on the information transformation and conservation laws [14].

Our concern for developing a cybernetic-informational pharmacology, as well as the important discoveries in the field of basic pharmacology, at both cellular and molecular level, allowed us to produce an "informational theory of dosage" [15].

Related to this theory, we also produced an introduction to the informational pharmacology of dosage [16, 17, 18].

In our research in experimental pharmacology, we initiated studies over a wide range of doses of a drug, highlighting the double-way, double-phase or even multi-phase effect of the homeopathic [19, 20, 21, 22] and allopathic [23] drug.

INTRODUCTION TO THE "INFORMATIONAL THEORY OF DOSAGE"

The message of the drug signal being codified in its chemical structure, the information derives not only from the nature of substance, but also from their order and organisation in space and time. Moreover, the information may change and diversify not only according to substance and energy quality, but also according to quantity. That means that the information carried by a certain structure quality, at various value scales of doses and concentrations may be different in terms of quality [15].

Information quality depends not only on the signal, but also on the receptor system. Information transfer may be understood only through the interrelationship between signal specificity and message intelligibility, required by decodification at receptor system level.

Modern cellular and molecular biology has been discovering types and subtypes of receptor systems [24]. The types correspond to certain structurally specific S.B. (mediators, hormones, etc.), while the subtypes differ according to the quantity of S.B. specific for the concerned receptor subtype. Thus, the human body multiplies the biological information and effects of S.B. Similarly, the double-way - stimulating and inhibiting - action produced by the same S.B. structure, but in different quantities, as well as concentration adjustment and indirectly, that of an S.B. effect, through its concentration itself, are possible.

Modern basic pharmacology discovers this informational aspect of doses in the case of M as well, being confronted with multi-phase, double-way effects of the same M at different doses.

Adding an "informational pharmacology of dosage" [16, 17, 18] to the informational pharmacology of structures, could restrict the area, the reactive substrate and the range of action of a drug, selectively, by choosing a certain category of a drug, selectively, by choosing a certain category of dosage, informationally significant for one single subtype of receptor system. This may open

new prospects for the high selectively of the pharmacotherapeutical action of M, a goal that hasn't been reached by pharmacology at the level of structural information yet.

Significant examples from modern cellular and molecular biology and from pharmacology are an evidence for and support this "informational theory of dosage".

ILLUSTRATION OF THE INFORMATIONAL THEORY OF DOSAGE IN PHYSIOLOGY AND CELLULAR AND MOLECULAR BIOLOGY

Adjustment through the feed-back cybernetic mechanism (retro-control), according to the concentration of the adjusted physiological parameter, has long been known in physiology and endocrinology.

Thus, we know that the function of endocrine gland secretion, i.e., thyroid, adrenal cortex, gonads, is governed by the blood concentration in the respective hormones and by the information brought by this concentration to the chemoreceptors in hypophysis or hypothalamus : this information may release, through an either positive or negative feed-back mechanism, the secretory level of the appropriate hypothalamic neural hormones or trophypophysary hormones which govern the necessary adjustment of the endocrine gland secretion. The adrenal cortex insufficiency syndrome, appearing as side effect of the abrupt interruption of a prolonged treatment with corticosteroids in pharmacological doses, is due to the inhibition of the adrenal cortex activity, determined by the impairment of the cortical-hypothalamic-hypophysary feed-back mechanism which, physiologically, regulates adrenal cortex secretion, as a result of the intensive administration of corticosteroids.

In the case of other endocrine glands (pancreas, parathyroid) the adjustment of the secretory function through a feed-back cybernetic mechanism is induced by the concentration of the gland-controlled biochemical parameter, i.e. the blood concentration level of glucose or calcium which provides a relevant information for the chemoreceptors in the respective glands.

This feed-back adjustment cybernetic mechanisms, informationally dependent on substance quantity, is updated by cell and molecular biology which demonstrates retrocontrol extension to the synaptic transmissions in the nervous system.

Thus, after the discovery of the "modulatory" presynaptic chemoreceptors, it was possible to understand the adjustment mechanism of chemical neuromediator concentration at the level of synaptic slots, through the information brought to these "modulatory" presynaptic receptors by the quantity of mediator itself existing in the slot at that time; these presynaptic receptors behave like real cybernetic "translators" releasing positive or negative "feed-back" mechanisms and encouraging the liberation and recapture of the slot mediator.

A well known example from cell neurobiology is the adrenergic synapsis, with beta and alfa-2 presynaptic receptors, functioning as modulatory "translators" of the

noradrenaline concentration in the synaptic slot and thus, indirectly, of adrenergic tonicity (Fig. 1).

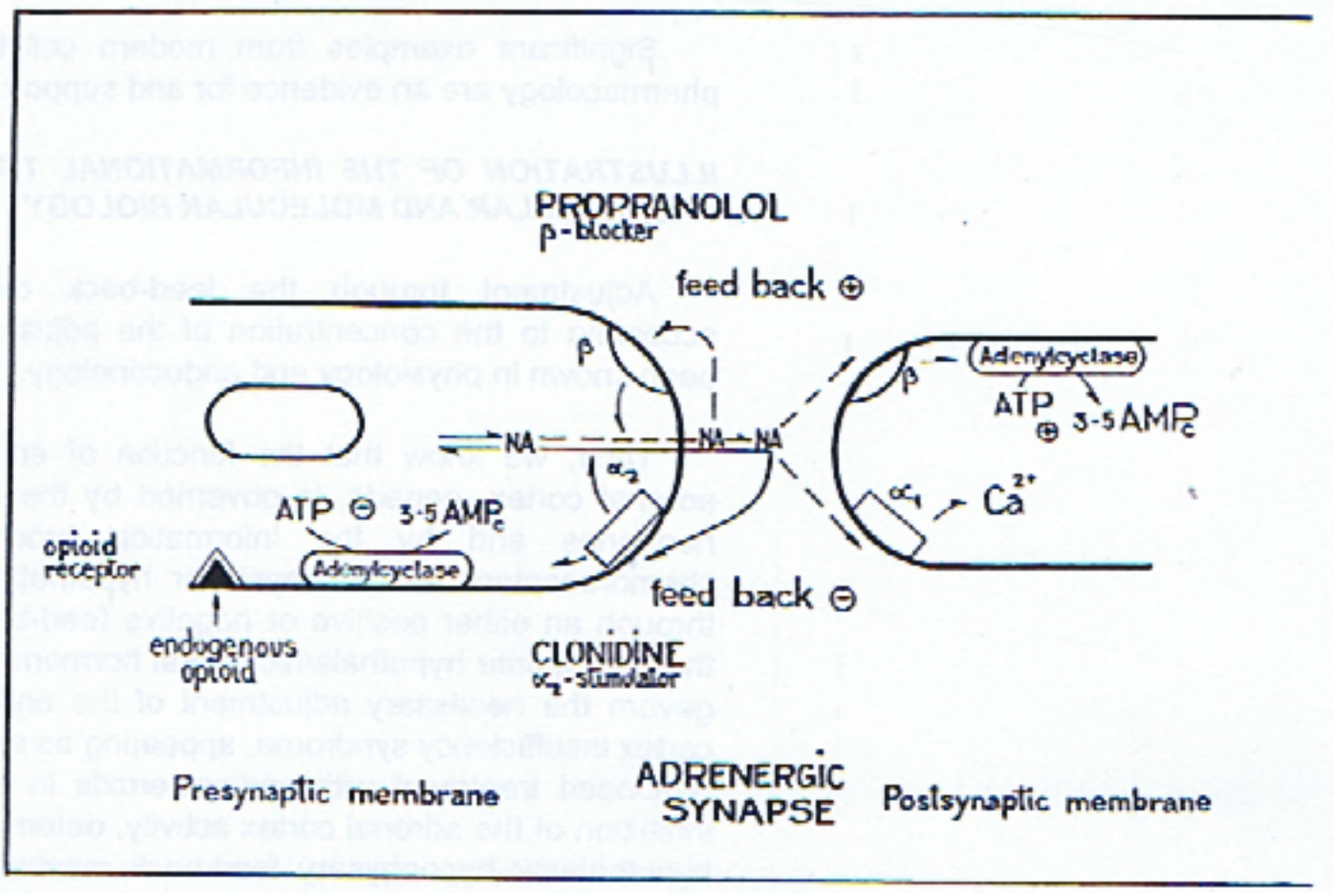

Figure 1

Adjustment of noradrenaline (NA) release and of sympathetic tone, according to concentration of NA released in the synaptic slot.

But, besides self-control through a cybernetic feed-back mechanism, molecular biology discovered an extremely interesting phenomenon, namely the double-way (stimulating and inhibiting) effect of a chemical mediator on the same function. This double-way effect of the same chemical structure can be explained through the "informational theory of dosage" and it is determined by the existence of subtypes of "effect" postsynaptic receptors, specific for a definite chemical structure, but "sensitive" to a certain quantity scale.

A long known example is the double-way vasodilator and vasoconstrictor effect of adrenaline, possibly through the stimulation of respectively beta-2 receptors at small doses and alfa-1 receptors at high doses.

Cell and molecular biology keeps discovering subtypes of "effector" postsynaptic receptors in every synaptic transmission [24], being thus able to explain the already known double-way effects of certain neuromediators and to highlight other effects unseized yet.

THE CASE FOR THE INFORMATIONAL THEORY OF DOSAGES IN MODERN BIOCHEMICAL BASIC PHARMACOLOGY

We emphasized the fact that M acts on the impaired cybernetic feed-before and feed-back mechanisms through 4 possible adjustment modalities, i.e. izo-, homeo-, alo- and enantioregulation. We pointed out that these 4 adjustment modalities are correlated with the type of chemical structure (information quality) of M, which might be identical, similar, derived or opposed with respect to the S.B. from the disturbed biological transmission [6, 11].

Considering the "informational theory of dosage", we insist on the importance of the ratio of the substantial to informational contribution of M, within these 4 disturbance adjustment modalities. Thus, in the case of izo- and homeoregulation, through an M identical or similar to the S.B. involved, substance quantity contribution/information quantity contribution ratio is below the unit, the required substance quantity contribution being low. In the case of a homeopathic drug, it is infinitesimal.

Comparatively, in alo- and enantioregulation, this ratio is naturally above the unit. In the case of the allopathic drug, this ratio is sometimes much higher than necessary, making it possible to appear undesired effects of the allopathic M, which, under these circumstances, becomes a polluting and disturbing element (P) for the biologic.

The different potencies of the same drug as compared to the various pharmacodynamic actions are well known in pharmacology. In other words, the various pharmacodynamic actions of a drug which appear at different doses are a known phenomenon.

For example, phenobarbital has an anticonvulsant - antiepileptic effect at doses lower than those inducing a hypnotic effect and even at subsedating doses.

Today, basic and informational pharmacology can explain this long known phenomenon in pharmacology, through the action of a chemical structure, depending on its quantity, on different receptor substrates at various organic levels and in various tissues.

In the case of phenobarbital, we know that besides the depressing action at the level of the upward activating reticulate formation, there is an action at the level of the receptor complex of GABA-ergic inhibiting synaptic transmission, enhancing the effect of GABA inhibiting neuromediator.

But, besides the pharmacodynamic actions with different potencies of a drug, a well known phenomenon in pharmacology, the double-way - stimulating and inhibiting - effect of a drug on the same physiological function is being highlighted as well.

We may talk of a modern updating of the classical but ingenious Arndt-Scultz Law. This Law asserts the existence of a relationship between the intensity of a stimulus and the intensity of its effect, involving the possibility of a change in the effect direction.

Thus, according to the Arndt-Schultz Law, a mild stimulus favours a function, a moderate one stimulates it, while a strong one depresses it. Thus, the Arndt-Schultz Law envisaged a change in the direction of the effect, from stimulating into depressing, according to the intensity of the stimulus.

This Law, known in classical pharmacology, perfectly explains dosage - effect relationship in the case of the stimulating non-specific drugs of SNC, both cortical (coffein, nicotine) and analeptic bulbar (pentetrazole type) or medular (strychnine type).

These stimuli, in therapeutic doses, stimulate S.N.C. activity, predominantly on a certain fragment, in toxic doses, the stimulus is overmaximal and irradiates inducing convulsions; while in lethal doses stimulation is replaced by depression (depletion of neuronal energetic resources) up to coma and, then, death.

But as pharmacological research develops both intensively and extensively, in connection with the effects of a wide scale of doses in a drug included, modern allopathic pharmacodynamics is faced more and more frequently with double-way - stimulating and inhibiting - effect, depending on the scale of doses used [23], a phenomenon well known in homeopathy [19, 20, 21, 22].

A very good example of the effect on plaquette aggregation process is acetyl salicilicum acid (ASA). The pathway of this effect is obviously dependent on dosage (Fig. 2). Thus, at small subanalgesic, antipyretic dose (0,5g every 2-3 dys) the effect is plaquette antiaggregating, while at medium, analgesic-antipyretic therapeutic dose (350 mg/day) and at high antiinflammatory doses (20 mg/kg every 12 hours) the effect becomes plaquette proaggregating. The explanation consists in the informational correlation between the different ASA doses and the specific reactive substrate involved in plaquette aggregation which decodes the signal message (Fig. 2). Thus, at small subanalgesic, antipyretic doses, ASA represents a specific signal only for cyclooxygenase in blood plaquette that it inhibits preventing the biosynthesis of plaquette thromboxane A2 (TxA2) with proaggregating function. While at medium and high analgesic, antipyretic and antiinflammatory doses, ASA represents a specific signal for cyclooxygenase in the vascular endothelium that it inhibits as well, preventing the formation of prostacycline (PGI_2) with plaquette antiaggregating function at this level.

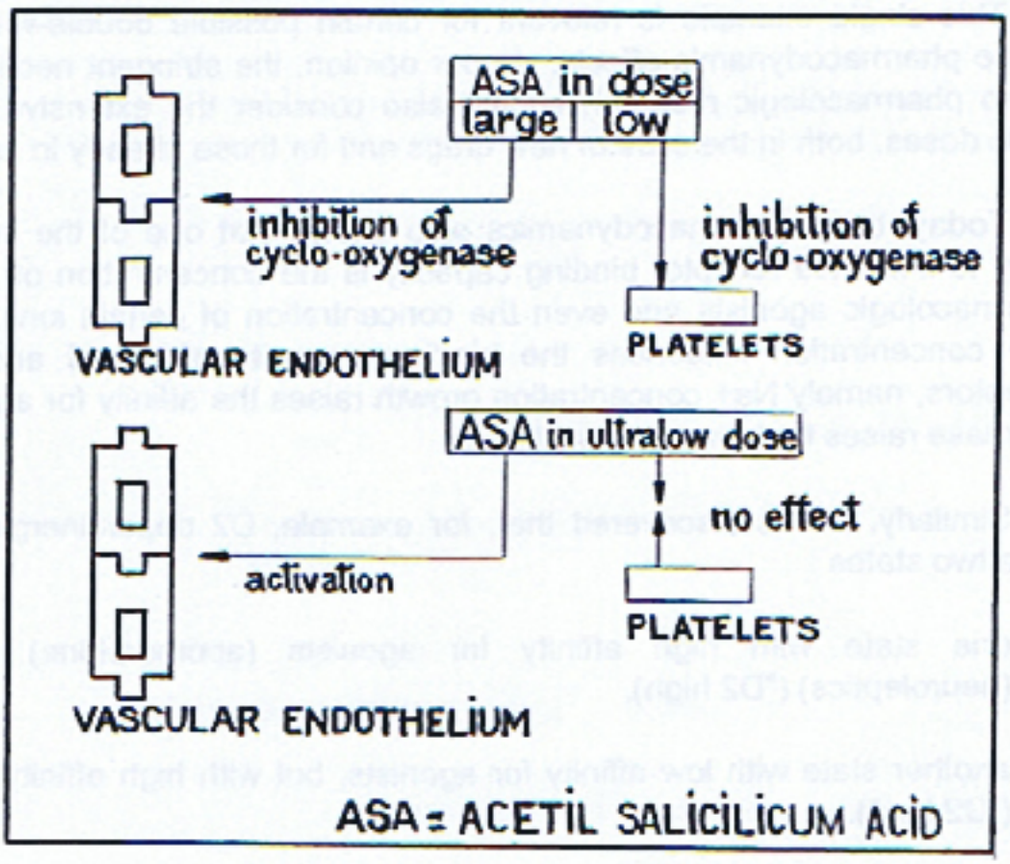

Figure 2

Informational relationship between acetyl salicilicum acid (ASA) and its reactive substrates, as a background to the informational mechanism of (ASA) plaquette antiaggregating effect.

Consequently, ASA is used as plaquette antiaggregant at small doses of 0,5g every 2-3 days (minimum 40 mg/day). But on the basis of the double-way effect, at high doses, it is quite possible that ASA should negatively influence plaquette aggregation, in a progaggregant direction; thus, it may be the iatrogenic drug cause of certain complications like thrombotic accidents, cerebral and ocular ischemic accidents, myocardial infarction, especially in patients at risk.

It is very interesting to mention that in the recent years it was discovered that at very low, plaquette subaggregating doses, ASA effect becomes plaquette proaggregating again. Research showed that at such almost infinitesimal doses, ASA does no longer acetylise cyclooxygenase irreversibly, blocking it; on the contrary, it liberates a proaggregating factor from the vascular endothelium, whose chemical structure is under study (Fig. 2).

It is very important to remember this change in the direction of acetyl salicilicum acid antiaggregating effect, at both high therapeutic and low subtherapeutic doses, for purpose of a strict observance of posology, when the plaquette antiaggregating effect of ASA is pursued.

This single example is relevant for certain possible double-way or just mult phase pharmacodynamic effects. In our opinion, the stringent necessity arises tha future pharmacologic research should also consider the extensive study of large scale doses, both in the case of new drugs and for those already in use.

Today, basic pharmacodynamics also knows that one of the important factor likely to influence receptor binding capacity is the concentration of physiologic an pharmacologic agonists and even the concentration of certain ions. For instance Na+ concentration influences the binding capacity of opioid and dopaminergi receptors, namely Na+ concentration growth raises the affinity for agonists, while it decrease raises that for antagonists [25].

Similarly, it was discovered that, for example, D2 dopaminergic autoreceptor have two states :

- one state with high affinity for agonists (apomorphine) or antagonist (neuroleptics) ("D2 high),
- another state with low affinity for agonists, but with high affinity for antagonist ("D2 low").

"D2 high" receptors answer to nonamolar (nM) concentrations of agonists o antagonists, while "D2 low" receptors are sensitive to micromolar (μM concentrations of agonists and nonamolar (nM) concentrations of antagonists.

This passage from a high affinity to a low affinity state is experimentally achieve through high concentrations of GTP. This passage occurs only for a limited numbe of "D2 high" receptors, not for all of them [25].

However, depending on their concentration, physiologic and pharmacologi agonists may regulate not only the binding capacity, but also receptor functionalit and number.

Thus, in addition to these double-way effects, modern cellular and molecula pharmacology has discovered receptor structure "sensitisation" and "desensitisation phenomena, according to the quantity of blocking antagonist or activator agonis drug. Based on these phenomena, modern pharmacotoxicology explains certai side effects of the drugs.

Tolerance, which consists in the diminishing efficacity of a drug administered i large quantities for a long time, is also due to pharmacoreceptors "desensitisation" through their "internalisation" in the membrane, as a reaction of protection towar informational aggression represented by agonist-type high-dose drugs and thei prolonged "repetition" (redundancy).

Thus, tolerance to beta-adrenergic (izoprenaline-like) bronchodilatin antiasthmatics, abusively used in bronchial asthma, appears, induced by a

desensitisation of the beta-adrenergic receptors in the smooth muscles of breathing bronchioles.

The "sensitisation" of pharmacoreceptors, represented by a growth in the number of exposed receptors outside the membrane, also explains side effects like abstinence syndrome and rebound effect induced by the abrupt interruption of the prolonged administration of certain drugs.

The clinical manifestation of the "rebound" phenomenon is disease exacerbation after interruption of treatment. This phenomenon is likely to appear when an antagonist-type drug blocked a type of receptors in a spatially and temporally disturbing way, and thus determined receptor "sensitisation", preventing receptor stimulation by the specific physiologic mediator. For purpose of preserving functional integrity, the system answers through a chemical mediator in excess (redundancy of specific S.B.). On interruption of treatment, the inertia of S.B. redundancy correlated with "sensitised" receptors may induce, for a certain time, the exacerbated clinical effects, known as "rebound" phenomenon.

The "rebound" phenomenon was mentioned, for example, on the abrupt interruption of the prolonged treatment with H2 histaminergic receptor-blocking antiulcerants (Cimetidine and Ranitidine), when the aggravation of gastro-duodenal ulcer may reach perforation.

Another example is the aggravation of angina pectoris after the abrupt interruption of the prolonged treatment with (propranotol like) beta-adrenolitics.

In the syndrome of abstinence to morphine, opiates and morphino-mimetics, an adrenergic-type symptomatology is predominantly manifest. This phenomenon should be understood as follows: in dependence on morphine, opioid receptors are overstimulated by the high quantities of morphinomimetic drug. Hence, the "modulator" effect of the endogenous opioid system (endorphins and encephalins) on the adrenergic "activator" system is brutally replaced by a really inhibiting effect. Therefore, through an informational adjustment between the two coupled systems, the quantity of adrenergic mediator released in the adrenergic synapsis is lowered and thus beta-1 adrenergic receptors in the cerebral cortex will be "sensitised", i.e. their number will grow while the quantity of biological adrenergic signal will diminish. When the administration of the morphinomimetic drug is abruptly interrupted, the adrenergic system, complementary to the opioid one, will brusquely resume its activity, releasing the biological adrenergic signal in large quantities and that one will noisily act on the "sensitising" adrenergic beta-1 receptors.

Consequently, in the syndrome of abstinence to exogenous opioids, symptoms of adrenergic system effect exacerbation will appear. Thus, in dependence on toxic drugs and in the drug abstinence syndrome we find a drug-induced impairment of the coupled and correlated activity of two complementary subsystems, i.e. the adrenergic and the modulator endogenous opioid systems.

In conclusion, we should emphasize the great practical importance of knowing drug effects and the various dose scales. As concerns the "informational theory of dosage" theoretically underlying this problem, it should be understood and approached at the level of the quantal-type dose-effect mathematical relationship.

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