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Correlations Between the Monoaminergic Status and the Psychoneuroendocrine Typology in a Murine Model – Possible Biomolecular Predictions for an Individualized Pharmacotherapy

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1. Introduction

The progress in the molecular pharmacology area continues to maintain a very alert rhythm at the beginning of the 3rd millennium. The volume of information accumulated in this area, with boundaries constantly expanding, as modern technology applied in current research which allows linking the imbalances manifested in the central nervous system metabolism with its various pathologies.

The neurons represent unique anatomical fractions, with the ability to forward the information in a network system, which justifies the experience-dependent mechanisms such as memorization, learning or consciousness. In order to fulfill these functions, the neurons are, structurally and functionally polarized. This aspect is obvious in their tripartite composition: cell body, axon and dendrites. While the body comprises the biosynthesis structure (nucleus, ribosomes, endoplasmic reticulum, Golgi apparatus and mitochondria for energy storage), the axon is equipped with molecular and under-cellular components for the propagation of the action potential from the cell body to distant targets, the dendrites represent a set of branched endings which prolong from the cell body and have as result an increase of it, in order to receive the signal. The structural connections for the signal transmission are the basis of the neural architecture. Inside the mature nervous system, normally, the neural circuit (neuro-architecture) supports adaptive changes. Inside an old synapses neural cells can involute (until their disappearance), with simultaneous formation of new branches (new neuritis) which will establish new synapses. These changes in the neurotic and synaptic architecture prove the great plasticity (capacity) of the nervous system to adapt to the environmental conditions. Today we consider that there are two major intracellular classes of factors (signals) which adjust the neuronal development and adaptation: growth factors (the growth factor - fibroblasts, the ciliary neutrophil factor, etc.) and the neurotransmitters factors (dopamine, serotonin, acetylcholine, glutamate, etc.). The loss of balance between the two systems of factors leads to the development of the pathological states.

The investigation of the central nervous system remains a fascinating field; it constitutes an inexhaustible source of new discoveries. The diversity of human nature and the uniqueness of the individual cerebral architecture lead to the exploration in this area on very subtle and difficult ways to analyze.

The individuality cell status, immune, genetic, etc., raised many questions, over time, and opened gates for new researches on human *polytypism.* Thus, under the action of identical factors, physical and emotional, the human beings develop different physiological, behavioral and emotional responses. This phenomenon was called **polytypism.** The phenomenon was inferred in 1980 by Rosenman RH who described, for the first time, the adrenergic behavioral type (type A).Lately, in the 1990s there was identified and described the opioid type (type O), the "non-A" type, opposite to the adrenergic type from the behavior point of view, and in 2000 the behavioral oncology has introduced the concept of C type, with genetic predisposition to the development of the biopsychosocial cancer.

In this context, the individualization of pharmacotherapy based on the psychoneuroendocrine typology, could be an important step for a specific medication, targeted and with fewer side effects. For this purpose, the molecular pharmacology researches in the world should bring evidences regarding the cellular, molecular processes which are the base of the pathophysiology for different psychoneuroendocrine types.

2. The psychoneuroendocrine behavior typology, factor of the biological and pharmacological variability

The differentiation of the adrenergic typology was first realized in 1978 by RH Rosenman, by describing some specific behavioral characteristics that predispose it to the emergence and the development of psychiatric and cardiovascular diseases: competitiveness, sharp ambition, continuous involvement in multiple and diverse activities, with a sense of haste and time urgency, irritability, impulsivity, reduced ability to disconnect and relaxation. Later, in the 1990s there was identified and described the "non-A" type, opposite to the adrenergics from the behavior point of view. Presently it is defined as the opioid type (O type), with the psychoneuroendocrine predominance of the endogenous opioid system. It has the following characteristics: defensive, calm, relaxed, non-aggressive, introverted, resistant to pain, but with predisposition to the hiperalgia post-stress syndrome.

The specialty literature describes several methods for identifying the A type of behavior in humans:

- **The structured interview (SI),** developed by Rosenman and Friedman (in 1978), in studies on mid-range employees. This interview contained a series of questions and followed: the volume of voice, the speed of response, the rhythm of the words, the latency of the responses, the gestures, the mimics, and the signs of hostility.
- **Self-assessment methods,** where the specialty literature includes:
  - **Jenkins Questionnaire (JAS)** contained 52 questions, similar with the structured interview and was developed by Jenkins in collaboration with Rosenman and Friedman;

- **Framingham Scale** contained 10 questions about the time urgency, the competitiveness and the motivation to work, the strong need to excel, the measures in which it feels dominated, the speed of eating;
- **Bortner grading scale** consisted of 14 questions and hass been extensively used in the European epidemiological studies;
- **Special Scale** useful for the identification of some particular features of A type (e.g. Interpersonal Communication).

3. Clinical and murine studies for investigating the adrenergic behavioral psychoneuroendocrine typology

The specialty literature describes numerous clinical and murine studies that have attempted to correlate the behavioral characteristics of A type with different physiological and biochemical parameters responsible for the onset of the psychiatric and cardiovascular diseases.

3.1 The cardiovascular reactivity

Numerous clinical studies (Appleton K.M) have been performed to correlate the characteristic features of A type with the cardiovascular responses, especially in stress. Thus, after the differentiation of individuals taken into study in groups of type A and type B (based on the Structured Interview validated by Rosenman, they were submitted to stressful situations (e.g. mental arithmetic exercises or unpleasant images displayed on a screen). They determined the following parameters: electrocardiogram, blood pressure, heart rate, peripheral vasoconstriction (the fingers). All studies have shown for the A type subjects exaggerated cardiovascular responses, in stress conditions.

Jones et al. investigated the variability of blood pressure in type A, related to the pleasure of victory. Thus, it was found that both victory and defeat, determined significantly higher cardiovascular responses for type A versus type B. The type A winners were distinguished from all other subjects by maintaining high levels of blood pressure and the type A losers have lost interest in competition.

It was also pursued in a study of 81 volunteers (published by Meesters C.M.G), the associatian between hostility and the risk of death by acute myocardial infarction. For comparison there were used a lot of subjects which had suffered a first myocardial infarction and a group which had no previous event. Following this study there was shown that the hostility was significantly associated with the risk of myocardial infarction, in people aged over 50 years.

In a clinical study conducted in the U.S.A., there was studied the generally individual sympathetic tonus of the type A individuals versus the ones of type B, by determining the pupil's diameter and also the platelet catecholamine concentrations (Powell L.H).

The study was conducted on 112 volunteers, differentiated on the basis of the Structured Interview. The individuals involved in the behavioral A typology were evidenced by a significantly higher adrenergic tone than on type B: higher pupillary diameter and high concentrations of platelet adrenaline.

In a study conducted in Canada there were followed, at individuals of type A, variations of the cardiovascular parameters after the administration, in bolus, a 50μg CCK-4 (cholecystokinin-tetrapeptid). This compound, administered in the shown manner, has the ability to produce symptoms of panic (panicogen agent). The variations of the heart rate, after the administration of CCK-4, were significantly higher in type A versus type B (Le Melledo J.M).

3.2 Pain sensitivity (endogenous analgesia)

Clinical studies (Cristea A) were conducted for evaluating analgesia and also the post-stress syndrome, in acute and chronic stress in type O compared with type A. Data reported in literature evoked the following:

- the basal pain sensitivity was significantly different in the two psychoneuroendocrine types (**hypersensitivity to pain for type A, compared with a painful hypo-sensibility in type O**);
- in chronic stress, the opioid becomes hypersensitive to pain and the adrenergic manifests depressive symptomatology.

3.3 Nervous behavior of types A and O

In a psychiatric hospital from Norway *(Haukeland University Hospital)* a clinical trial was conducted on 99 patients admitted for behavioral disturbances associated with depression (Oedegaard K.J). The patients were distinguished in lots A and B, based on the Jenkins questionnaire and there was followed the frequency of unipolar depression, bipolar depression and behavior depending on the type of migraine. The results of the study showed the following:

- the patients classified in the behavioral adrenergic typology were diagnosed with bipolar depression (in proportion of 65%);
- type A is characterized by a ciclotimic temper;
- the frequency of the migraine crisis was not significantly correlated with either type A or type B.

Comparative experimental studies have been conducted on animal behavior of type A and O, in pharmacological tests: the actometry test (for investigation the spontaneous motor activity), the platform test, the inclined plane test and the plate with holes test (to research the evasion-investigation behavior), the cross-maze test (for investigating the anxiety). These tests were performed on animal communities distributed on both psychoneuroendocrine typology and on gender (male of type A and male of type O, respectively on female of type A and O). The motor activity and the behavior of investigation were significantly higher in type A, the best results being recorded for the male animal communities (Cristea A). The cross-maze test revealed a significant predisposition to anxiety of the adrenergic type, regardless the gender.

Some authors speculated that the pathophysiological hallmark of type A individuals is the hyperactivity of the sympathetic nervous system, although the molecular basis of these findings have not been established, yet. It is therefore necessary to discern the intimate, molecular mechanisms determining both the susceptibility to certain diseases and a

pharmacotherapy of choice and with few side effects. From this point of view the pathogenic picture caused by the imbalance of the monoaminergic system becomes very important. Precise information regarding the different concentrations of monoamines in the cerebral tissue can bring considerable benefits to highlight the dynamics of these neuromediators. In addition, various therapies can change depending on the monoaminergic status for each individual.

3.4 Aim of the study

Based on these considerations, the researches conducted and presented in this paper were aimed to investigate the cerebral monoaminergic status of the adrenergic psychoneuroendocrine typology. Results were compared with the opposite psychoneuroendocrine type (type O) and with the intermediate, balanced, normal type (type N).

The paper presents an experimental model, on mice, to investigate the possible correlations between the behavioral psychoneuroendocrine typology and the brain levels of noradrenaline (NA), dopamine (DA), serotonin (5-HT) and γ -amino butyric acid (GABA). We used two different experimental contexts:

- correlations between the cerebral levels of the monoamines with the behavioral psychoneuroendocrine typology in **basal state**;
- correlations between the cerebral levels of the monoamines with the behavioral psychoneuroendocrine typology after exposure to **acute stress**.

4. Matherials and methods

4.1 Animals

Studies were conducted on 120 male, Albino Swiss mice, weighing 20-22 g. They were housed in a room and maintained at 25 ± 2^{o}C and 45-55% relative humidity, with an alternating 12h light-dark cycle. They had free access to food and water untill the morning of the experiment. All animals used in this study were maintained in facilities fully accreditated and the experiments described here were performed in compliance with the European Communities Council Directive of 24 November 1986 (86/609/EEC) and Ordinance No. 37 of the Romanian Government from 2nd February 2002.

4.2 Identification of the murine behavior type

Mice were divided in three behavioral groups, according to their reactivity to painful stimulus (endogenous analgesia): type A (associated with hypersensitivity to pain) and type B ("non-A", the opposite type of behavior) which exhibits hypo-reactivity to pain.

For the identification of the murine behavior type we used the hot-plate test (Ugo Basile apparatus). The plate was heated at 60 ^{o}C and the animals were divided, based on their reactivity to painful stimulus (endogenous analgesia, expressed as *jumping time off the heated plate*), into three working groups: the adrenergic "A" type, the equilibrated, intermediate,

"N" type and the "O" type, according to Gauss normal distribution curve. The average value (M) of the jumping time off the plate was established. Mice that possessed a value of the jumping time of M ± 1SD were selected as intermediate, "N" type. Mice that possessed the value of the jumping time less than M – 1SD (<M – 1SD) were selected as adrenergic "A" type, while the jumping time of more than M + 1SD (>M + 1SD) were selected as the "non-A" type ("O" type).

Acute stress was induced to animals using the classical forced swimming test. (Petit-Demouliere B.)

4.3 The assessment of cerebral monoaminergic status

Mice were sacrificed by decapitation and the whole brains were rapidly removed, weighed and kept at -80^{o}C until analyzed. Cerebral monoaminergic status (neuronal monoamines levels) within the behavioral model was evaluated by measuring the murine brain levels of noradrenaline (NA), dopamine (DA), serotonin (5-HT) using HPLC with UV detection, and γ-aminobutiric acid (GABA), using a fluorimetric assay. Results were expressed as μg neurotransmitter/mg wet tissue.

4.4 Simultaneous, HPLC evaluation of endogenous NA, DA and 5-HT

Samples were homogenized and deproteinized in 0.2M perchloric acid containing 100μM EDTA-Na_2. The homogenate was left for 30min. to deproteinize. Then, the homogenate was centrifuged at 10,000×g for 15min at 0^{o}C (Janetzki K24 cooling centrifuge). After centrifugation, the supernatant was adjusted to pH=3.35 by adding 1M acetic acid. 20μl were injected into an HPLC reversed–phase system (VARIAN – PROSTAR) with a Chromsep-Inertsil 5 OSD2, 250x 4.6 mm column. The mobile phase consisted of 0.8 mM EDTA-Na_2, 0.12M $NaH_2PO_4 \times H_2O$, 0.646g sodium heptane sulphonate and 17% methanol. Monoamines were detected simultaneously, using an UV detector (210nm).

4.5 Determination of endogenous GABA concentrations

Brain tissue samples were separately homogenized in 10 volumes of 0.01 M HCl using a glass homogenizer. The determination of endogenous GABA concentration is based on a fluorimetric assay that depends on the formation of a fluorescent product from the reaction between GABA and ninhydrin at alkaline pH and in the presence of glutamate. The reagents used in the assay were 0.05 M glutamic acid in 0.2 M sodium phosphate buffer, pH 6.4, 14 mM ninhydrin in 0.5M sodium carbonate buffer, pH 9.9-10 and copper tartrate reagent consisting of 1.6g Na_2CO_3, 329 mg tartric acid and 300 mg $CuSO_4 \times 5H_2O$, all made up in 1 liter of distilled water. 0.25 ml of homogenate was diluted with 0.25 ml of 0.01 M HCl and 0.5 ml of 10% trichloroacetic acid. This last reagent was used to precipitate the proteins. After the samples were centrifuged, 100 μl aliquots of the supernatant were added to 15 μl of glutamate solution and 200 μl of the ninhydrin solution. This mixture was incubated at 60^{o}C for 30 minutes and allowed to cool before the addition of 5 ml copper tartrate reagent. We also prepared two internal standards by adding to the samples of homogenate known amounts of GABA (50 μg and 100 μg GABA per sample) with the trichloroacetic acid.

5. Results and discussion

5.1 Assessment of the basal neuronal concentrations of noradrenaline, dopamine, serotonin and gamma-amino butyric acid on the adrenergic and opioid types of behavior

5.1.1 Distribution on psychoneuroendocrine murine groups

The researches were conducted on a community consisting of 100 mice. In the first stage was established the individual reactivity to pain of the entire group (n = 100) using the hot plate test. There have been registered the results of the individual reaction to pain expressed by the times of jump. Based on these experimental data there could be noticed that for the collectivity of animals tested for reaction to pain, the individual values of the times of jump ranged between 4 and 60 seconds, the average time of jump (Jt medium) was of 36.02 sec, and the standard deviation (SD) value was of 13.9 sec.

Depending on the individual reactivity to pain, the types of behavior were defined as follows:

- the adrenergic type (A), hypersensitive: Jt = 4-22 sec;
- normal, balanced type (N), normo-sensitive: Jt = 29-42 sec;
- the opioid type (A), hipo-sensitive: Jt = 50-60 sec.

The distribution of the animals from the researched collectivity, depending on the pain sensitivity is shown in Figure 1.

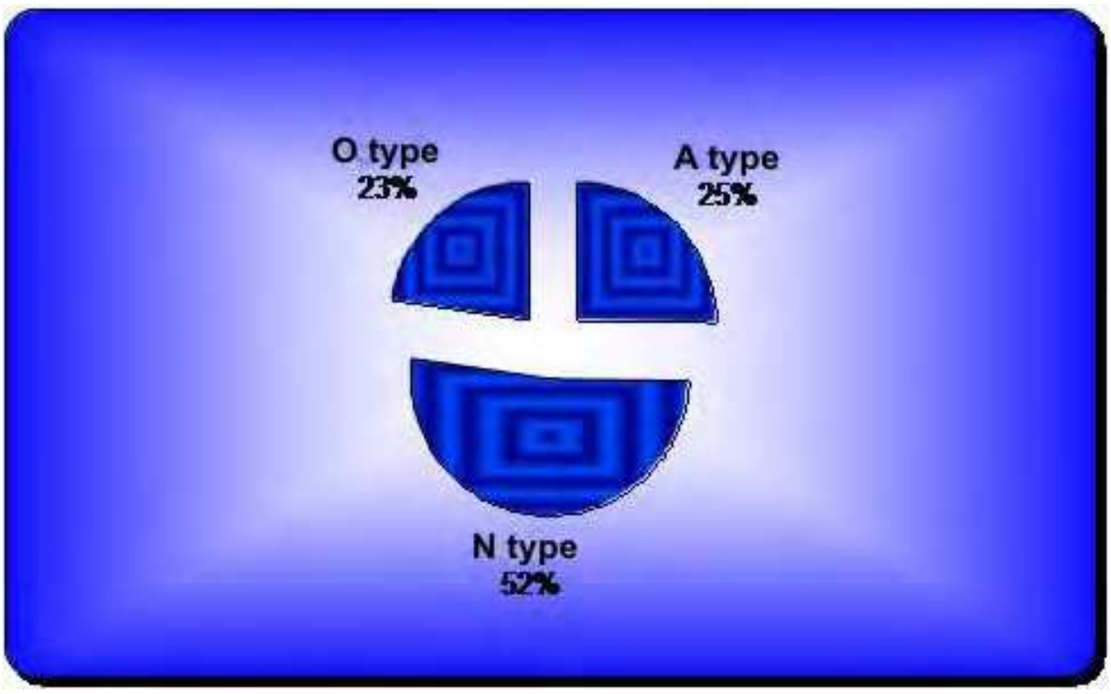

Fig. 1. The distribution of animals (n = 100) according to their pain sensitivity

The groups average values of the neuronal endogenous concentrations of noradrenaline (NA), dopamine (DA), serotonin (5HT) and GABA are shown in Table 1.

Behavior type	Cerebral concentration of the studied neuromediators in the basal state (µg/ mg wet tissue)			
	NA	DA	5HT	GABA
A type	1.01±0.189	0.67±0.2	0.12±0.005	1.14 ± 0.5
N type	1.04±0.11	1.02 ± 0.13	0.36 ± 0.09	0.70 ± 0.33
O type	1.52±0.26	1.1±0.01	0.53±0.01	0.54 ± 0.18

Table 1. The average values of the studied neuromediators, in basal state

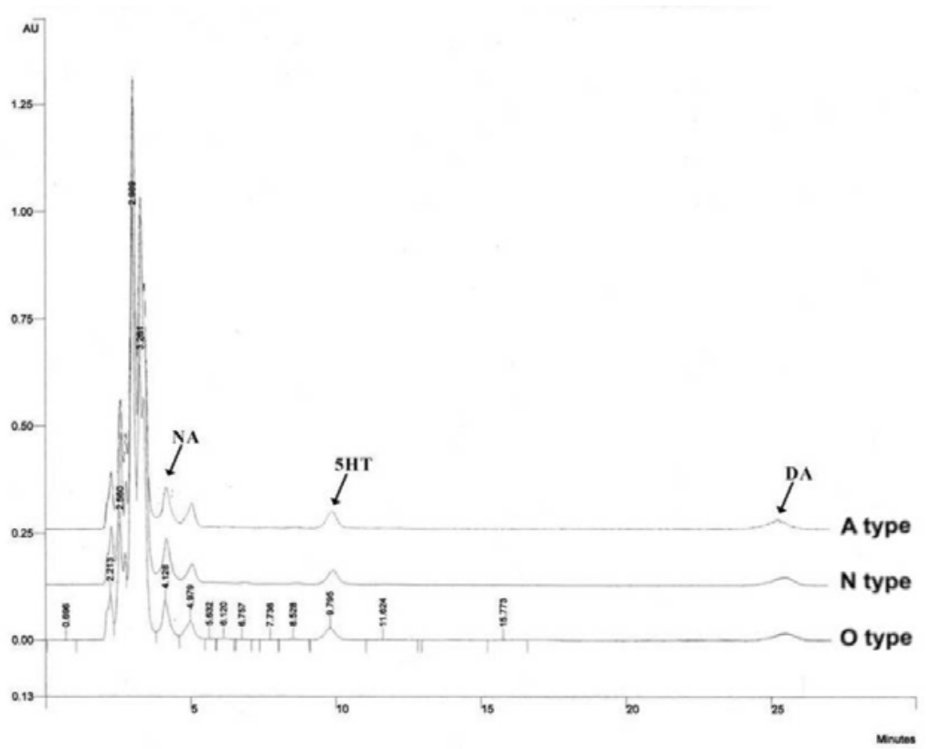

Fig. 2. Examples of chromatograms corresponding to types A, N and O in basal state

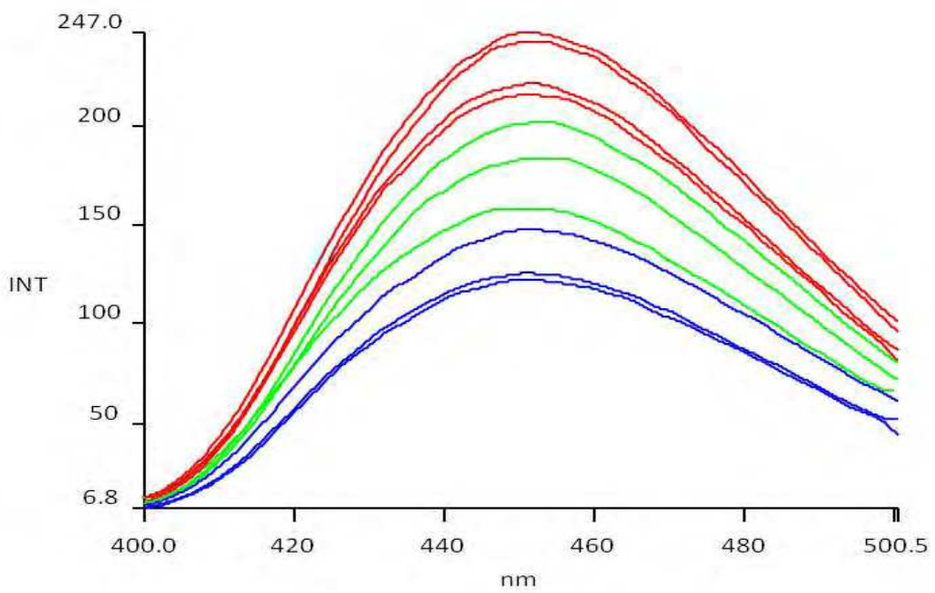

Fig. 3. Examples of fluorescence spectra corresponding to the neuronal endogenous concentrations of GABA in type A (___), type N (___) and type O (___)

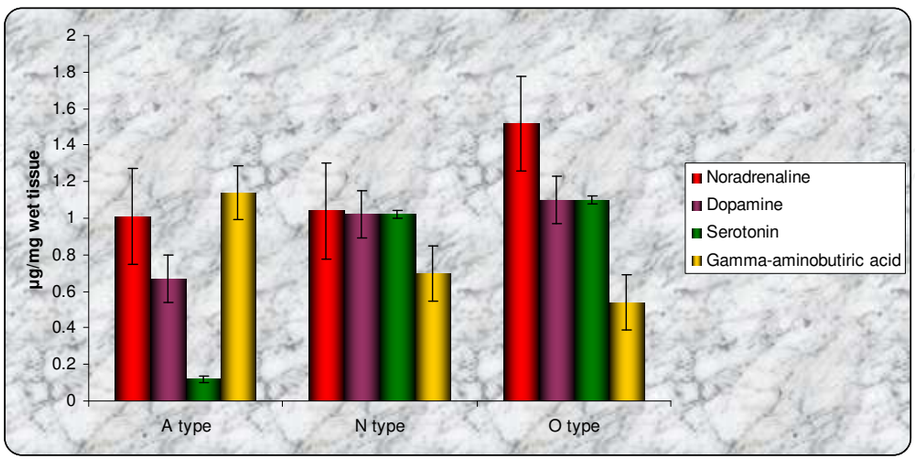

Fig. 4. The brain levels of the studied neuromediators, for the three murine behavioral types, in basal state

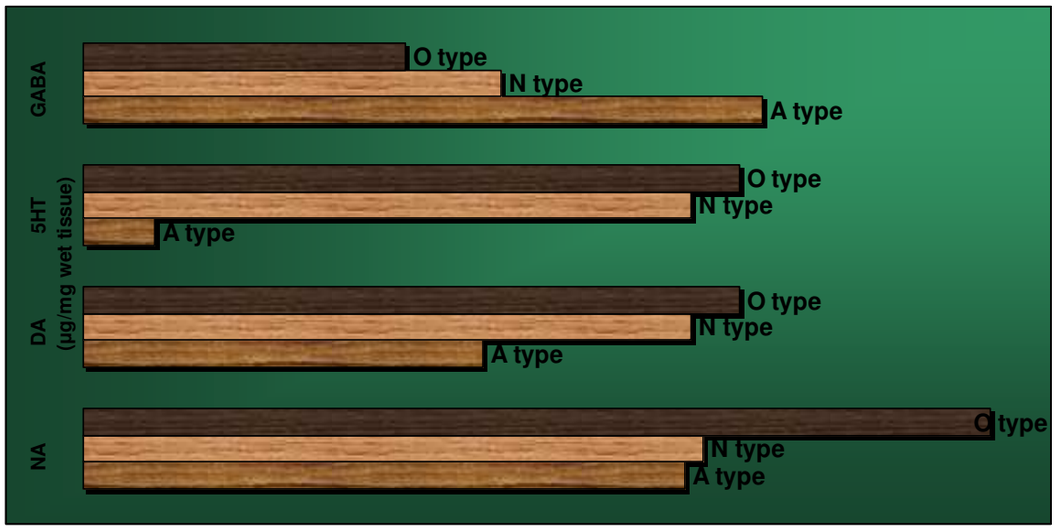

Fig. 5. Comparative assessement of the neuromediators neuronal concentrations studied, in brain, depending on the psychoneuroendocrine typology. Basal state

The status of the three types of basal monoaminergic psychoneuroendocrine studied concentrations was assessed by quantifying the neuronal noradrenaline, dopamine, serotonin and γ-amino butyric acid. Analyzing the experimental results highlighted the following issues:

- the neural dynamics of noradrenaline in basal state, has a maximum concentration in the opioid type (1.52 ± 0.26µg/mg wet tissue);
- there is a positive correlation (Pearson correlation coefficient r = 0.957) between the jumping time (a physiological parameter that describes the behavior typology) and a cerebral biochemical marker, namely the concentration of noradrenaline;
- both the adrenergic type and the balanced type releases much smaller amounts of noradrenaline, compared with type O (statistically significant): 1.01 ± 0.189µg/mg wet tissue, $p < 0.05$(type A) and the 1.04 ± 0.11µg/mg wet tissue, $p < 0.05$ (type N) (fig 5);
- the neural dynamics of dopamine in basal state, has a maximum concentration in the balanced type (1.02 ± 0.13µg/mg wet tissue), the recorded values being significantly higher than those recorded for the type A (0.67 ± 0.2µg/mg wet tissue , $p < 0.01$) and type O (1.1 ± 0.01µg/mg wet tissue, $p < 0.01$);
- the neural dynamics of serotonin in basal state, has a maximum concentration in the balanced type (0.36 ± 0.09µg/mg wet tissue), the recorded values being significantly higher compared with type O (0.53 ± 0.01µg/mg wet tissue, $p < 0.001$), especially compared with type A (0.12 ± 0.005µg/mg wet tissue, $p < 0.05$);
- the adrenergic psychoneuroendocrine type has a much higher concentration of GABA (fig 5), statistically significant (1.14 ± 0.50 µg GABA/mg wet tissue) compared with both the opioid type (0.54 ± 0.18 µµmols GABA / mg wet tissue, $p < 0.01$) and the intermediate type, balanced (0.70 ± 0.33 µµmols GABA / mg wet tissue, $p < 0.05$).

The GABA-ergic status varies inversely with the sensitivity to pain of the individuals from a population (Fig. 7), recording the maximum values for hypersensitive typology (Type A), Pearson correlation coeffient having a value of r = -0.9758.

It can be said therefore that the GABA-ergic transmission modulates, balances, in the basal state, the behavioral type "of warning", the adrenergic type.

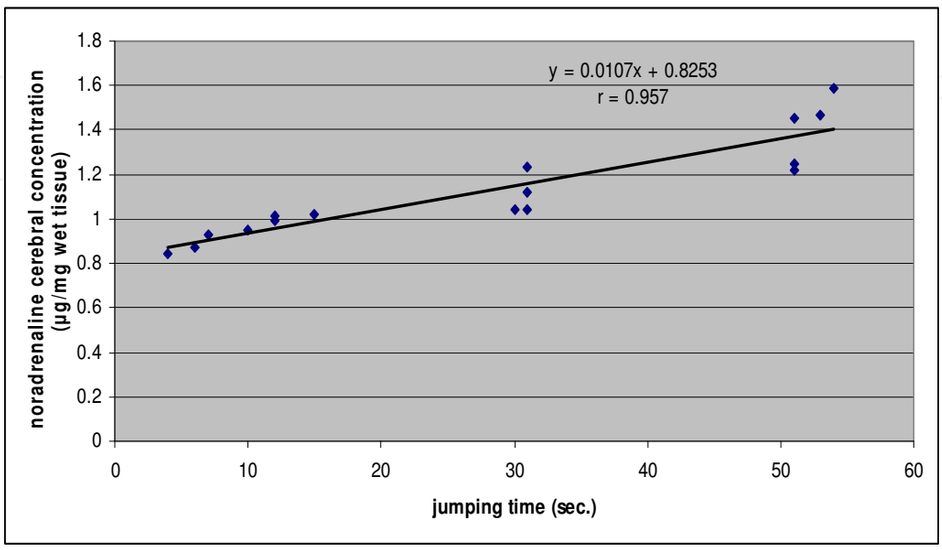

Fig. 6. Correlation between the jumping time and NA concentration for the three behavioral types

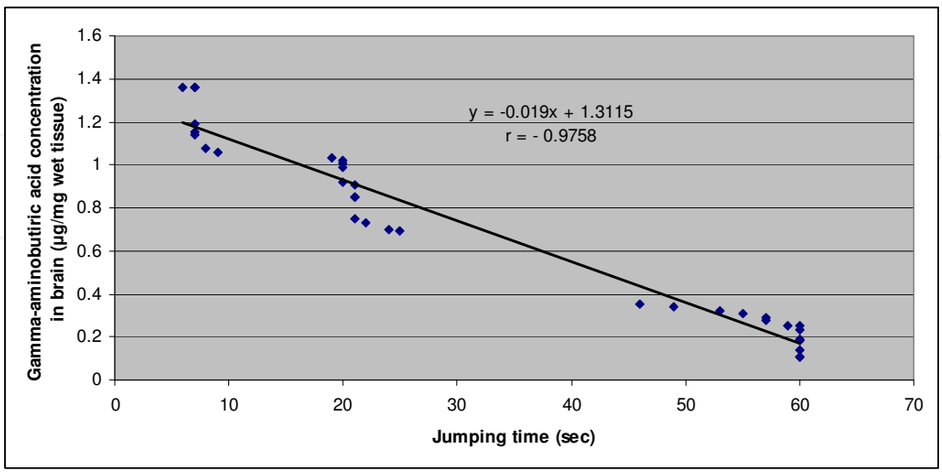

Fig. 7. Correlation between the jumping time and GABA concentration for the three behavioral types

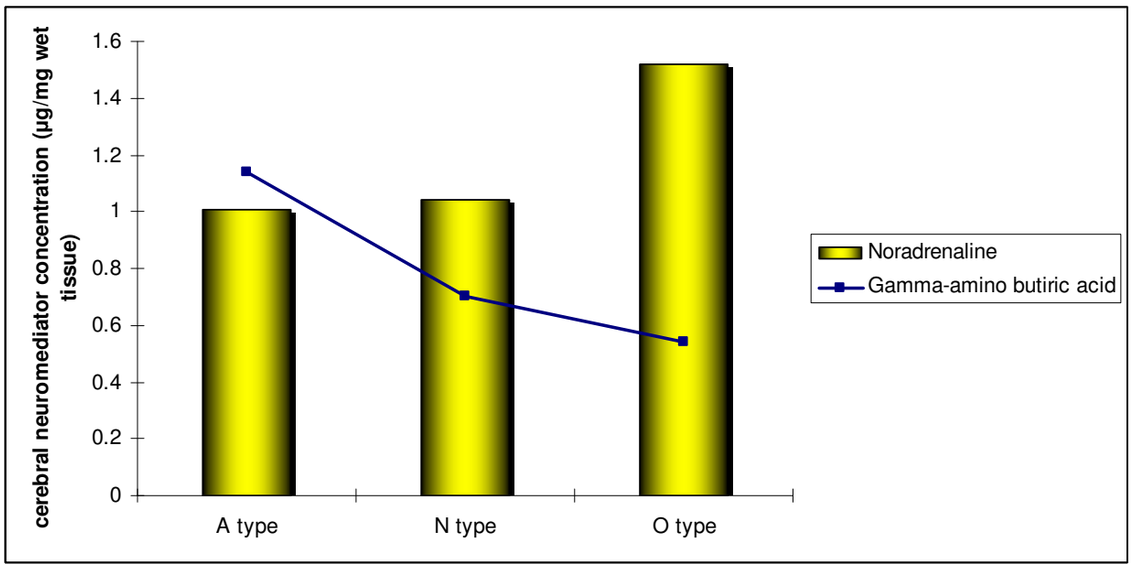

Fig. 8. Negative correlation between the basal neuronal concentrations of noradrenaline and γ-amino butyric acid , in basal state, for the the three murine behavioral types described (r = -0.9577)

The comparative analysis of the followed parameters (painful sensitivity - physiological parameter, expression of the psychoneuroendocrine typology and the neuronal concentrations of some biologically active monoamines - molecular biochemical markers) was able to reveal the following:

- in basal state, the adrenergic type (hypersensitive to painful stimuli) is not highlighted by a extremely high monoamine-ergic status, but is revealed as a very well balanced type, in this regard (high concentrations of both noradrenaline and γ-amino butyric acid);
- the opioid type, hipo-sensitive to pain, has also, unexpectedly, in basal state, the highest concentrations of noradrenaline in neurons, and large amounts of serotonin;
- in basal state, the balanced type releases the most large amounts of dopamine and serotonin.

5.2 Assessment of the neuronal concentrations of noradrenaline, dopamine, serotonin and gamma-amino butyric acid on A adrenergic and opioid types of behavior after acute stress

5.2.1 Distribution on psychoneuroendocrine murine groups

The researches were conducted on a community consisting of 100 mice. In the first stage was followed the individual reactivity to pain of the entire group (n = 100) using the hot plate test. There have been registered the results of the individual reaction to pain expressed by the times of jump. Based on these experimental data there could be noticed that for the collectivity of animals tested for reaction to pain, the individual values of the times of jump ranged between 4 and 60 seconds, the medium time of jump (average medium Jt) was of 36.04 sec and the standard deviation (SD) value was of 15.85 sec.

Depending on the individual reactivity to pain, the types of behavior were defined as follows:

- the adrenergic type (A), hypersensitive: Jt = 4-20 sec;
- the normal, balanced type (N), normo-sensible: Jt = 29-42 sec;
- the opioid type (A), hipo-sensible: Jt = 52-60 sec.

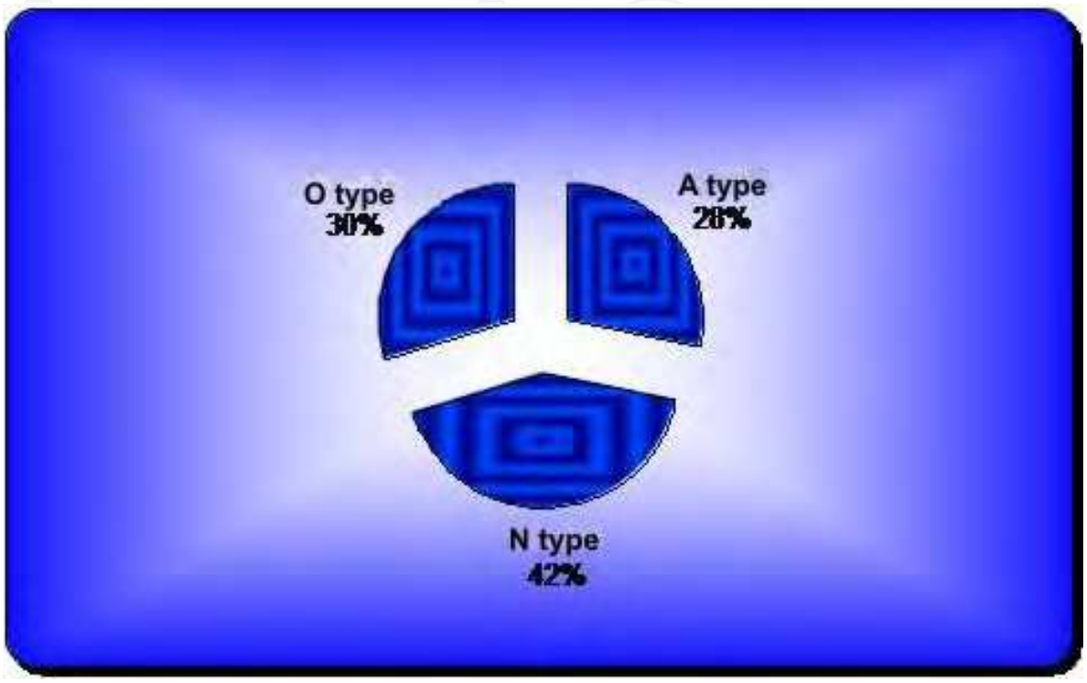

Fig. 9. Distribution of animals (n = 100) according to pain sensitivity

The acute stress was induced through the forced swimming test, the test of "desperation". After the 6 minutes of forced swim, each animal was sacrificed, the cerebral tissue was isolated and the biological material was processed to determine the concentration of the neuromediators NA, DA and 5HT by HPLC with UV detection.

Behavior type	**Cerebral concentration of the studied neuromediators after inducing acute stress (µg/ mg wet tissue)**			
	NA	DA	5HT	GABA
A type	3.41 ± 1.14	0.13 ± 0.03	0.12 ± 0.05	1.55 ± 0.77
N type	1.59 ± 0.24	0.32 ± 0.12	0.45 ± 0.13	1.52 ± 0.55
O type	1.55 ± 0.13	0.25 ± 0.05	0.47 ± 0.1	3.15 ± 0 .68

Table 2. The average values of the studied neuromediators, after acute stress

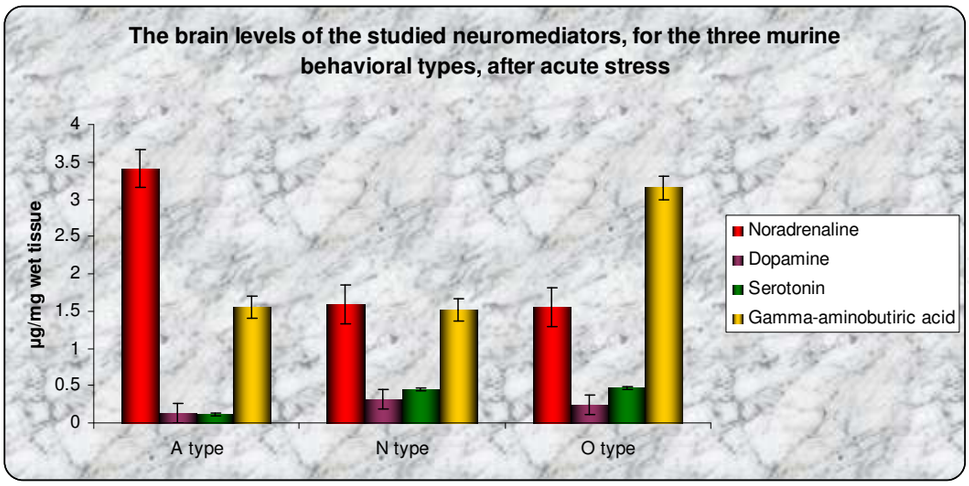

Fig. 10. The brain levels of the studied neuromediators, for the three murine behavioral types, after acute stress

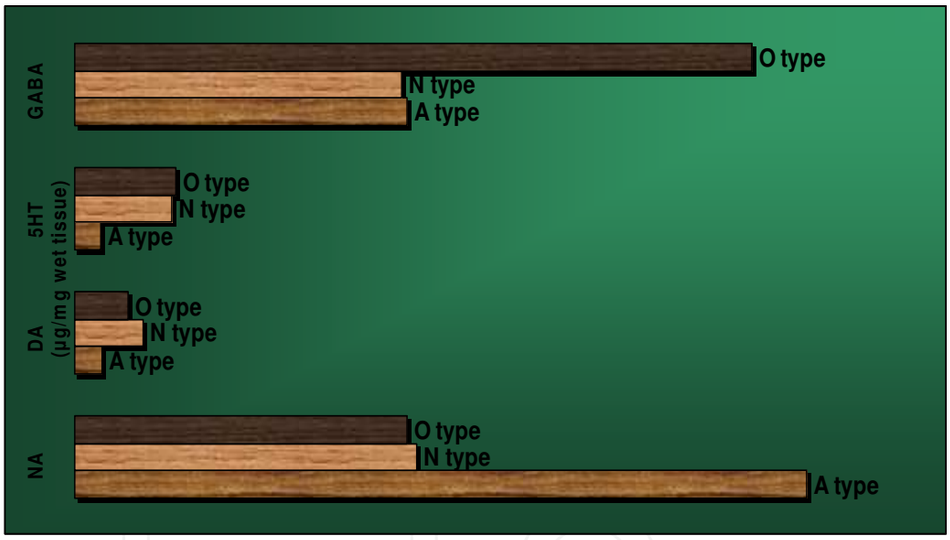

Fig. 11. Comparative assessement of the neuromediators neuronal concentrations studied, in brain, depending on the psychoneuroendocrine typology. Acute stress

The assessment of the monoaminergic status of the three psychoneuroendocrine types after acute stress highlights the following:

- in acute stress, the adrenergic type releases, in neurons, the largest amounts of noradrenaline (statistically significant) (3.41 ± 1.14µg/mg wet tissue) compared with type N (1.59 ± 0.24µg / mg wet tissue), but especially compared with type O (1.55 ± 0.13µg/mg wet tissue, $p < 0.01$);
- type A it also developes the lowest amounts of γ-amino butyric acid , its concentrations being negatively correlated with those of noradrenaline (r=-0.9345, fig.y);
- the balanced type releases, in acute stress, the highest quantities of dopamine, the dynamic of this neuromediators varying in the following order: type A (0.13 ±

0.03µg/mg wet tissue, p <0.000001) <type O (0.25 ± 0.05µg/mg wet tissue , p <0.001) <type N (0.32 ± 0.12µg/mg wet tissue);

- the neuronal dynamics of serotonin, in stress state, has a maximum concentration in the opioid type (0.47 ± 0.1µg/mg wet tissue), the recorded values were significantly higher compared with type A (0.12 ± 0.05µg/mg wet tissue; p <0.01); the balanced type, in turn, revealed higher values of serotonin concentration (0.45 ± 0.13µg/mg wet tissue) compared with type A.
- the opioid psychoneuroendocrine type has a much higher concentrations of GABA, statistically significant (3.15 ± 0,68 µg GABA/mg wet tissue) compared with both adrenergic type (1.55 ± 0.77 µg GABA/mg wet tissue, p <0.001) and the intermediate balanced type (1.52 ± 0.55 µ/mg gwet tissue, p <0.001).
- our data showed a positive correlation (r = 0.9584) between the neuronal levels of serotonin and GABA after inducing acute stress in the O type of behavior. (fig. 13).

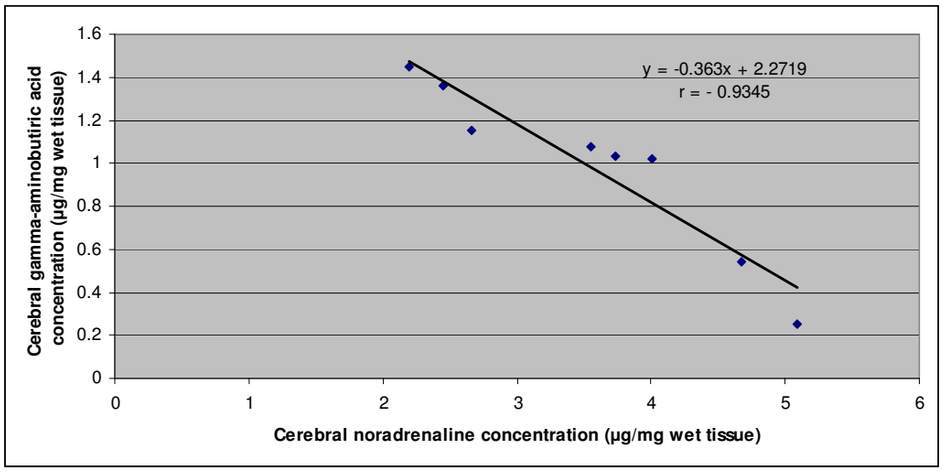

Fig. 12. Negative correlation between neuronal concentrations of of noradrenaline and γ-amino butyric acid , for the A type, after acute stress

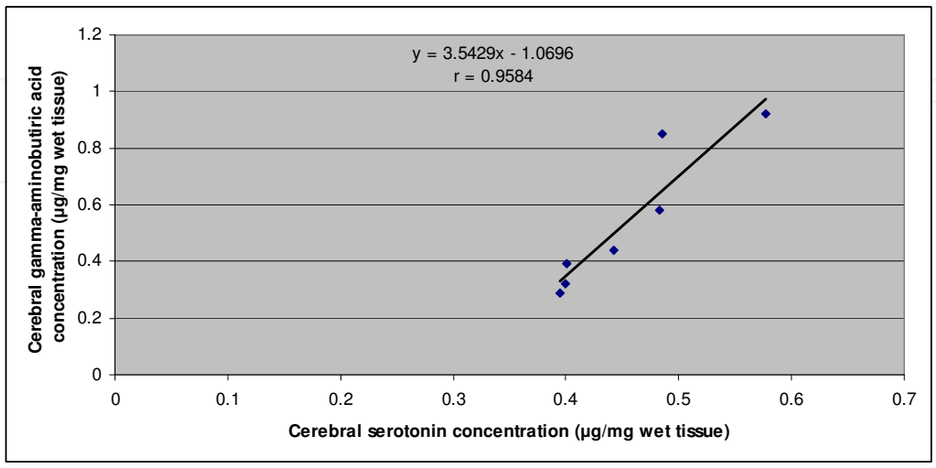

Fig. 13. Positive correlation between neuronal concentrations of of serotonin and γ-amino butyric acid , for the O type, after acute stress

After the induction of acute stress, the two followed parameters (painful sensitivity - physiological parameter, expression of the psychoneuroendocrine typology, respectively, the status of the monoaminergic-molecular biochemical marker) revealed some notable observations:

- in acute stress, the adrenergic type biosynthesis and releases the largest quantities of noradrenaline;
- the opioid type releases, in stress, gamma-amino butyric acid and serotonin.

The comparative assessment of the dynamics of the neuronal concentrations of noradrenaline (NA), dopamine (DA), serotonin (5-HT) and γ-amino butyric acid (GABA) in basal state and after acute stress, is shown in Figures 14-17.

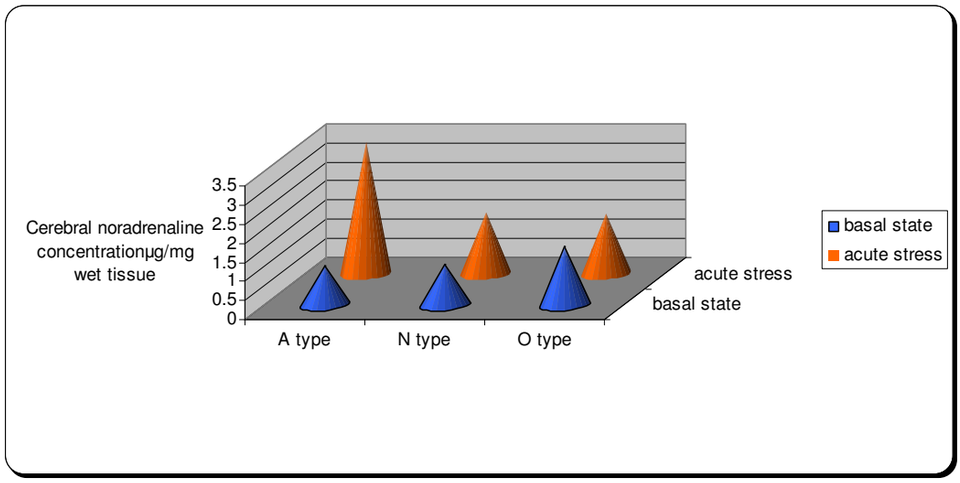

Fig. 14. Dinamics of brain concentrations of noradrenaline in basal state and after acute stress, for the studied behavioral typologies

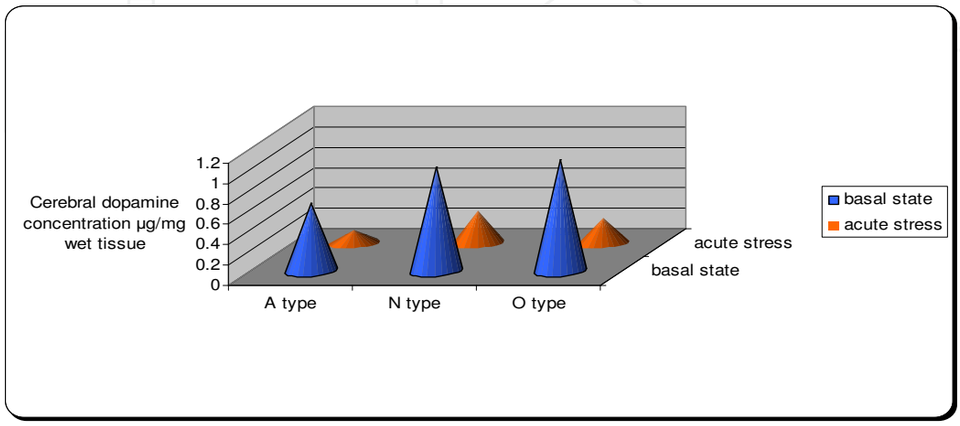

Fig. 15. Dinamics of brain concentrations of dopamine in basal state and after acute stress, for the studied behavioral typologies

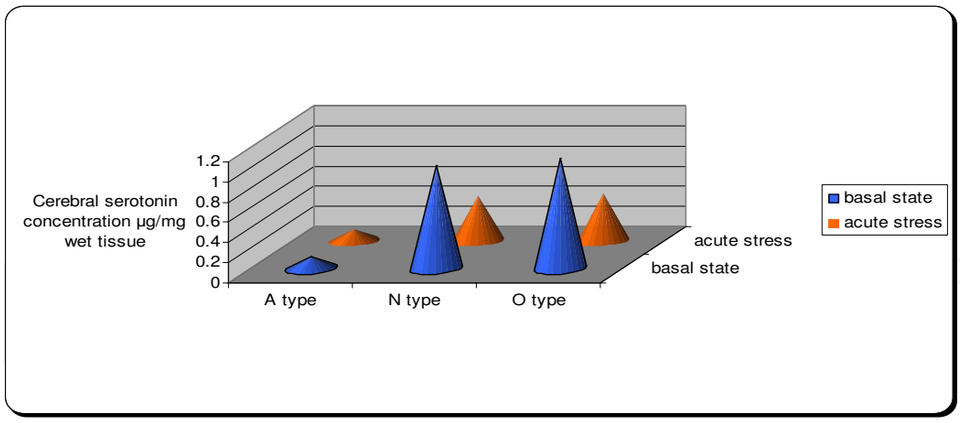

Fig. 16. Dinamics of brain concentrations of serotonin in basal state and after acute stress, for the studied behavioral typologies

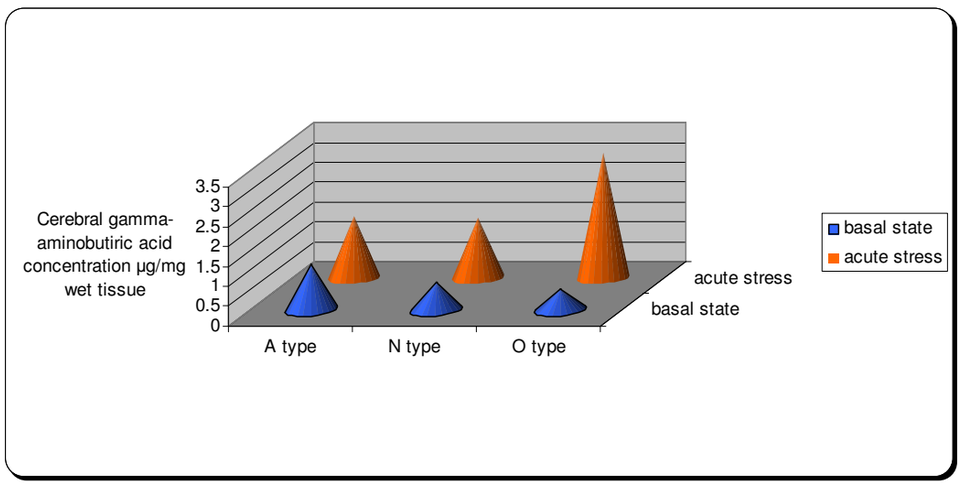

Fig. 17. Dinamics of brain concentrations of γ-amino butyric acid in basal state and after acute stress, for the studied behavioral typologies

6. Conclusion

The experimental study presented proves, once again, the great biological variability and brings new information on the molecular mechanisms that maintain the homeostasis of the central nervous system. From this point of view, the psychoneuroendocrine typology reveals itself as a major factor of the pharmacological responses to drugs with action on the monoaminergic transmission.

The different therapies might suffer changes (might be improved) to optimize the pharmacological response by the criterion of the psychoneuroendocrine typology. The clinical observations reported in the literature, pathologies associated to typologies and the pharmacologic response to various drugs possess a high degree of subjectivity, requiring intimate, molecular discerning mechanisms which cause both susceptibility to various diseases, and appropriate therapy.

From this point of view, the researches presented reveal molecular information, which can maintain and complete the clinical and experimental data reported in the literature. Thus, the type A, characterized by a behavioral point of view by alert, rush, speed, hostility, aggressiveness, is proving extremely balanced in terms of basal neural mechanisms. The basal monoaminergic tone of type A is stable and maintained in moderate limits (high levels of noradrenaline, together with high levels of γ-amino butyric acid–the main inhibitory neuromediator of the CNS). We can say that, in the basal state, the adrenergic type, though alert and active in terms of behavior, is balanced and protected at the molecular level by the inhibitory GABA-ergic mechanisms.

The intervention of the stress factors distorts, however, in the adrenergic type, these balance mechanisms (activating/inhibiting), against the inhibition mechanisms (protection), by releasing extremely large quantities of noradrenaline, together with low amounts of γ-amino butyric acid.

This could be one of the possible observations of molecular pharmacology which prones the A type vulnerability to stress (with the pathological consequences reported in literature).

In contrast to the adrenergic type, the O type of behavior offers surprising observations. It developed high neuronal concentrations of NA in basal state (much higher than for type A), but with no psychosomatic effect. It seems that the opioid type does not use important cellular concentrations of noradrenaline, its molecular mechanisms being modulated, probably by endogenous opioids. In stress, it is modulated (beside the endogenous opiates) through serotoninergic pathways (high serotonin levels) together with an extremely high GABA-ergic status. In addition, the acute stress does not lead, for type O, to substantial fluctuations in the amount of cerebral noradrenaline, compared with basal condition. It is quite possible for the opioid psychoneuroendocrine type to be behavioral modulated, by an interrelation between the endogenous opioid system with the triptaminergic (serotoninergic) system.

These experimental data lead, naturally, to the following question: *why some individuals cellulary use more noradrenaline, while others use endogenous opioids? Is there, perhaps, a "preference" of the neurons for certain neuromediator?* A possible answer might be found in modern theories of the substrate receptors resistance (e.g. the assumption of the resistance of the insulin receptors, which explains the etiopathology of type 2 diabetes). Thus, it is quite possible that the adrenergic receptors of type O are resistant to noradrenaline, while the opioid receptors of type A are resistant to endogenous opioids.

Our hypothesis is sustained by the researchers of the serotonin type of behavior. by using the modern technology of the positron emission tomography (TEP), they have shown that these individuals framed by questionnaires of personality in the serotoninergic typology, have a large number of $5HT_{1A}$ receptors. Extrapolating this observation to types A and O, it might appear the hypothesis of the existence of a significant variation of the adrenergic receptor density, respectively, opioids among the individuals of a population.

The neural dynamics of the monoaminergic mediators for extreme typologies (A and O) is confirmed by the results of the intermediate, balanced type, which biosynthesizes and releases, in stress, all the researched neuromediators, in large quantities. There is also a special preference of the intermediate N type for using dopamine as a biomolecule of stress.

The paper provides molecular evidences that support and argue the theory of the pharmacological variability, due to the psychoneuroendocrine typology (as a part of the biological variability), and bipolar disorder is included within. A review seeking to identify the more consistent findings suggested that there are several genes involved in the development of bipolar disorder (Serretti A., 2008), such as those for serotonin (SLC6A4 and TPH2), dopamine (DRD4 and SLC6A3) and excitatory neuromediators (DAOA and DTNBP1). There is also a the theory asserting that people developping bipolar disorder experience a series of stressful events, each of which lowers the threshold at which mood changes occur (Brian Koehler et al). There are also reported evidences of neuronal abnormalities in bipolar disorder due to stress. Published clinical studies, reported the prevalence of bipolar disorder within the adrenergic behavioral type.

In this sense, the imbalances of the monoaminergic systems, which may lead and/or sustain bipolar disorder require, certainly, an individualized pharmacotherapy on the criterion of the psychoneuroendocrine typology.

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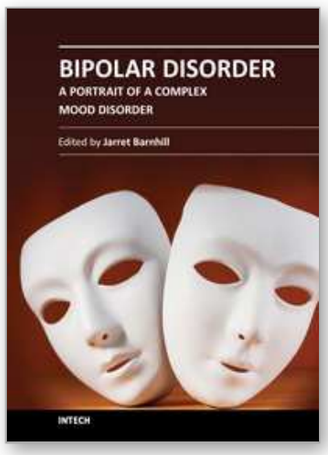

Bipolar Disorder - A Portrait of a Complex Mood Disorder
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Bipolar Disorder: Portrait of a Complex Mood Disorder is a step towards integrating many diverse perspectives on BD. As we shall see, such diversity makes it difficult to clearly define the boundaries of BD. It is helpful to view BD from this perspective, as a final common pathway arises from multiple frames of reference. The integration of epigenetics, molecular pharmacology, and neurophysiology is essential. One solution involves using this diverse data to search for endophenotypes to aid researchers, even though most clinicians prefer broader groupings of symptoms and clinical variables. Our challenge is to consolidate this new information with existing clinical practice in a usable fashion. This need for convergent thinkers who can integrate the findings in this book remains a critical need. This book is a small step in that direction and hopefully guides researchers and clinicians towards a new synthesis of basic neurosciences and clinical psychiatry

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