We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

4,800
Open access books available

122,000
International authors and editors

135M
Downloads

Our authors are among the

154
Countries delivered to

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities

CLARIVATE ANALYTICS BOOK CITATION INDEX INDEXED

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

Chapter 1

Murine Models for Developping an Individualized Neuropsychopharmacotherapy Based on the Behaviour Typology

Andreea Letitia Arsene, Niculina Mitrea,
Dumitru Lupuliasa, Cristina Manuela Dragoi,
Alina Crenguta Nicolae, Ion-Bogdan Dumitrescu,
Dragos Florian Ciolan and Doina Draganescu

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/53323

1. Introduction

A drug administered in the same dosage, under similar conditions, to adult individuals from a population homogeneous in race, gender and age, triggers different pharmacological effects. This phenomenon represents the pharmacological variability in a relatively homogeneous population, as a natural expression of the biological variability of the response to any stimulus. The cause of the pharmacological variability to a drug is often considerably different between the individuals of the same population. The pharmacology variability (pharmacokinetics, pharmaco-dynamics and pharmaco-toxicological) is therefore of two types: inter-individual (on population level) and, respectively, intra-individual (on individual level).

General mechanisms of the pharmacological variability

They can be grouped into: pharmacokinetic mechanisms (variations in the drug concentrations in the plasma and in the substrate receptor) and pharmaco-dynamic mechanisms (variations regarding the drug-receptor substrate complex).

Pharmacokinetic mechanisms of the pharmacological variability

The variations in the drug concentrations in plasma and on the level of the receptor substrate represent the pharmacokinetic variability which contributes to the pharmaco-dynamic, pharmaco-therapeutic and pharmaco-toxicological variability. The cases are represented

by inter and intra-individual differences, in the rate of the physiological processes: absorption; distribution (transport, diffusion, storage); epuration (biotransformation, excretion).

The most extensive and complex pharmacokinetic variability is manifested in the biotransformation process, being caused by the following phenomena: enzyme induction or inhibition, induced by various factors including by the inducing drugs or enzyme inhibitors; enzymopathies genetically determined.

Pharmaco-dynamic mechanisms of the pharmacological variability

The variations regarding the complex drug- receptor substrate induce the pharmaco-toxicological and pharmaco-dynamic variability. The causes are represented by inter-intra-individual differences, in the functional state of the receptor system (R) - the effect on the number and the binding capacity of R, the state of intermediate links in the chain of the receptor-effector system and to the physiological agonist concentrations (chemical mediator) and certain ions in the R level.

The biological variability in the functional state of the receptor-effector system is determined by the following phenomena: desensitization of R ("down" - adjustment) or sensitization of R ("up" - adjustment), caused by various factors, including the agonist drugs and the antagonists drugs or of illnesses of the receptors (autoimmune diseases, genetic diseases, aberrations induced by mutagens and oncogenes drugs, diseases of the link of coupling R – effector, represented by Gs protein).

The types of pharmacological variability

In accordance with these multiple mechanism generating individual reactivity on the drug effect, the pharmacological variability can be classified into several types:

- By the criterion of the area of expansion of the population: inter-individual and intra-individual variability.
- By the criterion of the appearance time: congenital and acquired variability;
- By the criterion of the statistical classification: normal, uni-modal variability (Gaussian type) and abnormal (bimodal or multimodal).

From a statistical viewpoint (reported on the average response of most individuals), the pharmacological variability is manifested either uni-modal (Gaussian) or polimodal.

- *The normalvariability* depends on the physiological type (CNS type, endocrine, metabolic, etc.) and on the ability to physiological control the enzyme functions (induction and enzyme inhibition) and the receptors ("up" and "down" adjustment). The normal relationship between the intensity of the pharmaco-dynamic effect (the response) and the number of the individuals from a community which respond with the same intensity, on the same dose of medication, it is represented in Cartesian graph by the frequency-distribution curve.
- *The abnormal variability* is the consequence of the genetic diseases (receptoropaties and enzymopathies) or the immunological mechanisms (allergic and autoimmune). In this case, the normal frequency-distribution curve with the allure of a bell looks bimodal, trimodal or even multimodal.

http://dx.doi.org/10.5772/53323

Psychoneuroendocrine behavior typology, factor of the biological and pharmacological variability

The psychoneuroendocrine typology should be considered within the factors generating biological and pharmacological variability. We refer to the following two types of psychoneuroendocrine behaviours, described in literature:

- the adrenergic type "A". 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 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.
- the opioid type "O". The “non-A” type, opposite to the adrenergic type from the behavior point of view, 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.

Based on the studies performed and published by Rosenman RH on the adrenergic psychoneuroendocrine type (A) [30], numerous experimental and clinical studies have been performed to highlight the neuroendocrine grounds of the opposite behavioral type, usually called type B or “non-A". In this regard there was hypothesized that the "non-A" type has, in fact, opioid neuroendocrine bases and was suggested as type "O". This hypothesis was based on the following theoretical and practical considerations:

1. The endogenous opioid system (through a cybernetic mechanism of "feedback" type) operates as a modulator system of the activator, "alarm", adrenergic (operating through a cybernetic mechanism of "feed-before" type) systems. Between these two systems there are highly complex interrelationships, their non-synchronization or physiological alterations resulting in different pathological conditions such as the coronary disease or cardiac ischemia. It was also shown that stress, adrenaline and endogenous opioids act through some very well correlated mechanisms [8].
2. Pharmacological research has shown that the adrenergic system and the endogenous opioid system are closely-correlated and involved in the informational aggression syndrome [7,8]. Thus, it was shown that there are two types of individuals: those who have the *adrenergic type of behavior* associated with *basal pain hypersensitivity*, and others having the *opioidergic type of behavior* associated with *pain hyposensitivity* [8].

Therefore, in order to differentiate the human and murine adrenergic and opioid types, the literature presents the following methods:

- for human subjects: personality questionnaire - personality type O was found to be opposite (complementary) to type A, corresponding to type B (“non-A”);
- or humans and animals: the reaction to pain - it should be registered the time for the pain reaction occurrence by using the heat stimuli.

Parameter followed	*Type A*	*Type O*
1. Hostility	1.1 Hostile	No
	1.2 Irritable, angry	No
	1.3 Aggressive	Defensive
	1.4 Agitated	Relaxed
	1.5 Randy	Calm
	1.6 Extroverted	Introvert
2. The spirit of competition	2.1 Fighter	No
	2.2 Ambitious	No
	2.3 Dominant	No
	2.4 Confident	No
	2.5 Deep involvement in an activity, failing to distraction	No
	2.6 Hyperactive	Slow
3. The urgency of time	3.1 Hurry	Calm, slow
	3.2 Tense	Relaxed
	3.3 Alert	Fear
	3.4 Strained countenance	Relaxed
4. Appetite	4.1 Great (increases in stress)	Anorexia

Table 1. Personality questionnaire for differentiating typologies A and O [7]

Assessment of the behavioral type of adrenergic type in children [13,16]

The clinical trials have included children of different ages (3-13 years) being included both boys and girls. There were pursued the following parameters:

- the time in which the child likes to play;
- the impatience;
- the competitiveness;
- the anger;
- the aggressiveness;
- the crisis time;
- the cardiovascular response (the systolic blood pressure, the diastolic blood pressure, the heart rate);
- the variation of the urinary catecholamine concentrations in basal and stress state.

These studies highlighted that the characteristic features of A type can be measured from the early childhood (3-6 years). It was also noted that boys obtained higher scores for the A type behavior, compared with the girls. In addition, the cardiovascular responses and the urinary concentrations of catecholamines were much higher in boys than in girls, both in basal state and in stress.

The assessment of the behavioral type of adrenergic type in men and women [13,14]

http://dx.doi.org/10.5772/53323

The specialty literature describes numerous clinical studies that have attempted to differentiate the adrenergic feminine typology by the male typology. In this respect it was found that the sex factor does not significantly influence the personality traits specific to adrenergic, major differences occurring with the installation of stressful situations. Thus, it was found that in stress, the systolic blood pressure, the heart rate and the urinary catecholamine levels are significantly lower in women than men. Basically, the women's physiological reactivity is much less competitive than the men's, in the same stressful situation.

Clinical studies on the impact of A Type behavior on the cardiovascular physiological reactivity.

Numerous clinical studies have been performed [14,16,17,19] to correlate the characteristic features of A type with the cardiovascular responses, in stress. Heart rate, EKG, blood pressure and peripheral vasoconstriction were mesured. Type A individuals revealed increase cardiovascular responsiveness.

Clinical studies for investigating the physiological reactivity of A type with sympathomimetic or sympatholytic drugs [13,27,29].

There were carried out numerous research studies of the cardiovascular responses (systolic and diastolic blood pressure, heart rate), in individuals with personality of type A, treated with beta-adrenolitic. The results showed that these drugs reduced in type A statistically significant cardiovascular physiological parameters investigated, compared with type B.

A number of clinical studies investigated the antagonistic potency in sympathetic/parasympathetic systems in type A, compared with type B. In this purpose were evaluated the specific cardiovascular parameters (e.g. the amplitude of T wave from electrocardiogram) after the administration of sympathomimetic drugs (isoproterenol, norepinephrine, etc). In all cases the return to normal, physiological limits of the studied cardiovascular parameters was achieved much faster (significant) in type B, suggesting a lower parasympathetic antagonism in the adrenergic type.

Murine and clinical studies on the impact of A Type behavior on the CNS physiopathology

Published clinical studies, reported the prevalence of bipolar disorder and the ciclotimic temper within the adrenergic behavioral type [2,3,7].

Experimetal 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), were performed on animals. Their results revealed a significant predisposition to anxiety of the adrenergic type together with an higher agitation [7].

In our previous studies [2] we evaluated the cerebral monoaminergic status, in mice identified as adrenergic or opioid types, compared with the intermediate N type. We mesured the neuronal levels of noradrenaline, serotonin, dopamine and GABA, both in basal state and after acute stress in order to establish some potential predictive biomarkers for an individualized therapy according to the behaviour typology.

2. Objectives

Individuals variability in regard to their reactivity to thermic stimuli constitutes an accepted predictive factor for establishing the behavioural typology in animals [8] namely the adrenergic and opioid types. Thus, the reported validated murine model is the hot-plate test. Accordingly, the jumping time off the 60°C heated plate characterizes animals' endogenous analgesia: the A type of behaviour is associated with basal pain hypersensitivity, while the O type correlates with pain hyposensitivity.

Therefore, after the endogenous analgesic screening, mice were divided into three working groups: the adrenergic "A" type, the equilibrated, intermediate, "N" type and the "O" type, according to Gauss normal distribution curve.

The murine models described were used for investigating the thymic tonus in scute stress, the circadian cronovariability of the thymic tonus and the variability of the antidepressant effect of imipramine, fluoxetine and lithium.

- Studies regarding the thymic tonus in acute stress to adrenergic and opioid types
- Circadian cronovariability of the thymic tonus, within each psychoneuroendocrin type
- Research of the variability of the antidepressant effect of imipramine, fluoxetine and lithium to adrenergic and opioid psychoneuroendocrine types

3. Matherials and methods

Animals

Five-week-old Albino Swiss male mice were purchased from the Biobase of "Carol Davila" University (Bucharest, Romania). They were housed five per cage at a room temperature of 25 ± 1 ºC and 45-55% relative humidity with free access to food and water. Mice were maintained under standardized 12h light-dark cycle (lights on at 7a.m., lights off at 7p.m.) for 1 week before the experiments. 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.

Identification of the murine behavioral type

For the identification of the murine behavior type the hot plate test (Ugo Basile apparatus) was employed, previously described. Briefly, mice were behaviourally characterized based on their endogenous analgesia expressed as the jumping time off the 60 ºC heated plate. Three murine behavioural working groups were drawn: the adrenergic A type (with low endogenous analgesia, low pain reactivity – including thermic pain stimuli), the opioid O type (high endogenous analgesia, high pain reactivity) and the intermediate N type.

Forced swimming test (FST)

http://dx.doi.org/10.5772/53323

To investigate the acute stress-related activity within the murine behavioural categories described, the forced swimming test (FST) was used as stressor (immobilization stress). The procedure was performed according to a previous report (Porsolt et al., 1977). Briefly, mice were placed individually into plastic cylinders (height, 25cm; diameter, 10cm) containing 10 cm of water maintained at 21-23 ºC, and left there for 5 min. A mouse was considered to be immobile when it floated in an upright position and made only small movements to keep its head above water. The duration of immobility was recorded during the 5-min testing period.

FST was also used to establish, within the three murine behavioural typologies described, a pharmacological response pattern after the administration of some psychotropic drugs.

Drugs and treatment procedure

Imipramin, fluoxetin and lithium carbonate were purchased from Sigma. Other routine reagents were of the highest purity commercially available. The drugs were dissolved in sterilized saline. To investigate the influence of the drugs on mice behaviour (expressed as immobility time during the FST), groups of 10 mice from each behavioural typology were injected intraperitoneally, for 10 days, at 9 a.m., the following doses: saline, imipramin 10mg/kg, fluoxetin 10mg/kg, lithium carbonate 70mg/kg. The animals were subjected to the FST before and after drugs administration.

Statistical analysis

For the statistical analysis of the data there were used one-way ANOVA, Spearman coefficient and Pearson coefficient. (SPSS software).

4. Results and discussion

Identification of the murine behavioral type

Individuals variability in regard to their reactivity to thermic stimuli constitutes an accepted predictive factor for establishing the behavioural typology in animals, namely the adrenergic and opioid types. Thus, the reported validated murine model is the hot plate test. Accordingly, the jumping time off the 60 ºC heated plate characterizes animals' endogenous pain responses (endogenous analgesia): the adrenergic type of behavior was associated with basal pain hypersensitivity, and the opioidergic type of behavior was correlated with pain hyposensitivity.

The average value of the jumping time off the 60 ºC heated plate was 30.8±5.36sec. Mice that possessed a value of the jumping time (Jt) of M ± 1SD were selected as intermediate, N type. Mice that registered Jt< M – SD were selected as adrenergic A type, while Jt>M +1SD marked the non-A type (O type) mice.

The differential physiological effects (endogenous algic response) after exposure to the 60 ºC heated plate resulted in a statistical significant difference between A and O type ($p<0.001$), Spearman correlation=0.9812. (figure 1).

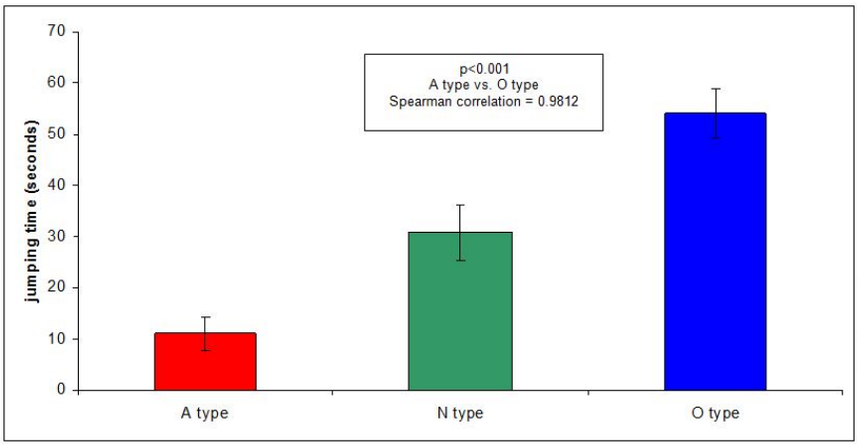

Figure 1. The establishment of the behavioural typology in animals according to the differential physiological effects (endogenous algic response) after the exposure to the 60 ºC heated plate (hot plate test)

According to the hot-plate test, the group of animals was distributed as follows (figure 2):

- 30% adrenergic mice;
- 37% normal,intermediate mice;
- 33% opioid animals.

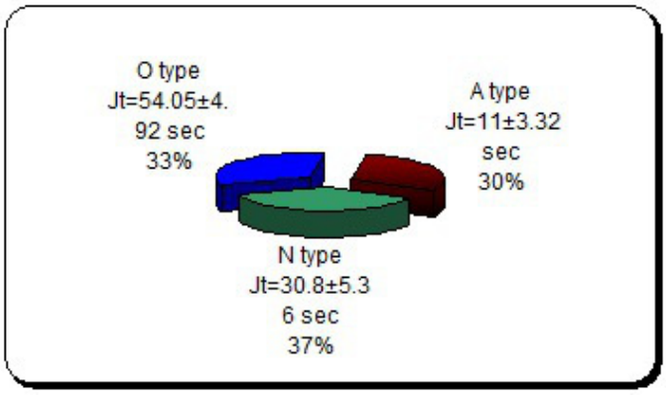

Figure 2. The distribution of the studied animals according to their pain sensitivity

The behavioural screen of the adrenergic and opioid murine typologies after acute stress

The literature shows that, under stress, the clinical manifestations depend on the balance between the adrenergic system and opioid endogenous system [7,8]. For these reasons, under stress, there is great behavioral variability of the psychoneuroendocrine types A and O. This aspect has been shown by means of complex clinical tests, where types A and O have been exposed to the sustained chronic stress. The research results have shown a significant tendency of type A towards the depressive syndrome, in case of the advanced chronic stress. Assuming that the adrenergic, psychoneuroendocrine behavioral type is characterized by competitiveness, combativeness and alertness, we proposed to assess the thymic tonus of

http://dx.doi.org/10.5772/53323

adrenergic type, in comparison with the opioid type, under acute stress induced by forced swimming ("desperation") test.

Each individual from each group was submitted to FST and results are depicted in figure 3. As it can be seen the immobilization time is higher in the O type (90.5±23.77 sec), compared with both the A type (37.6±10.64 sec; $p<0.001$) and N type (81.9±15.54 sec; $p<0.05$).

	A type	N type	O type
Jt (sec)	11±3.32	30.8 ±5.36	54.05 ± 4.92
Timob(sec)	37.6 ± 10.64	81.9 ± 15.54	90.5 ± 23.77

Table 2. The average values of the jumping time off the heated plate (Jt) and the immobility time (Timob) during FST for the studied behaviour types

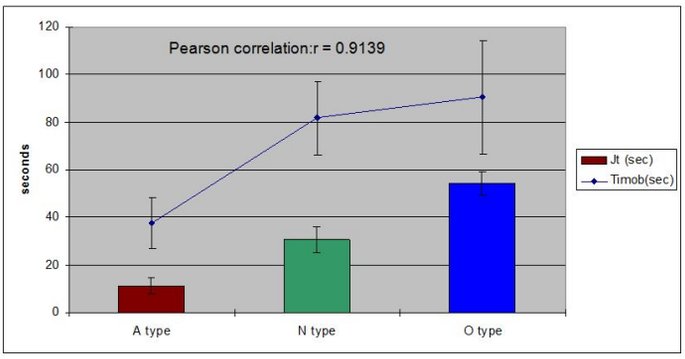

Figure 3. Correlations of the results obtined after submitting the animals to the hot plate test and the forced swimming test

One-way Anova revealed a significant different behavioural reactivity (expressed as immobility time) between the A, N and O groups ($F=3.037$; $p< 0.001$). Eventhough the frequency of immobility counts (seconds) is lower for the adrenergics, the A type pattern of the swimming behaviour during FST positively correlates with the O type (Pearson coefficient = 0.9139).

Cronovariability of acute stress-related behavioural patterns

The circadian change of the acute stress responsiveness during FST, related to the adrenergic and opioid behaviour patterns was registered hourly, between 9 and 13 a.m. FST is a consummatory behavioural test in which the homeostatic control of the animal's stress responsiveness and adaptation depends both on the neuronal excitability and neurondocrine reactivity. Previous studies reported an enhanced glucocorticoid and mineralocorticoid responses for the A type of behaviour, together with a high norepinephrine and epinephrine status during specific cognitive tasks, which postulated the basis of psychophyysiological mechanisms of high blood pressue, ischemic cardiopathy, myocardial infarction and sudden death. Recent studies also reported low urinary free cortisol levels togetherwith high urinary norepinephrine excretion in patients with endogenous type depressive disorder, bipolar disorder, paranoid schizophrenia(). All these reports may seem contradictory, but, in fact,

many studies reported that the hypothalamic-pituitary-adrenal (HPA) axis plays a pivotal role during organisms adaptation to stress. There was also reported that the activity of HPA axis is influenced by pschychological factors (conflict, the sense of control, etc.) which act through the corticosteroid/catecholamiergic receptor system within the hippocampus.

Neuroendocrine studies have shown that glucocorticoids, mineralocorticoids and catecholamines regulate the stress-activated neural metabolism, modulate the stress response and control the subsequent adaptive behaviour of animals [4,5,10,26]. There was demonstrated that a proper balance between glucocorticoids, mineralocorticoids and catecholamines is of paramount importance for the homeostatic control of organisms' stress and adaptation.

In this regard, we aimed to assess the acute stress behaviour profile of the A type, compared with both the the opioidergic O type and the normal N type, during FST.

In order to assess the chronovariability of the thymic tonus in the three psychoneuroendocrine types, the initial communities of animals corresponding to types A, N and O have been redivided, as follows:

- Group 1A: consisting of adrenergic type animals, for which the immobilization time was monitored between 9-10 am
- Group 2A: consisting of adrenergic type animals, for which the immobilization time was monitored between 10 to 11 am
- Group 3A: consisting of adrenergic type animals, for which the immobilization time was monitored between 11 to 12 am
- Group 4A: consisting of adrenergic type animals, for which the immobilization time was monitored between 12 to 13 pm
- Group 1N: consisting of intermediate, balanced type of animals, for which the immobilization time was monitored between 9-10 am
- Group 2N: consisting of intermediate, normal type of animals, for which the immobilization time was monitored between 10 to 11 am
- Group 3N: consisting of intermediate type of animals, for which the immobilization time was monitored between 11 to 12 am
- Group 4N: consisting of normal type animals, for which the immobilization time was monitored between 12-13 pm
- Group 1O: consisting of opioid type animals for which the immobilization time was monitored between 9-10 am
- Group 2O: consisting of opioid type animals for which the immobilization time was monitored between 10-11 am
- Group3O: consisting of opioid type animals for which the immobilization time was monitored between 11-12 am

http://dx.doi.org/10.5772/53323

- Group 4O: f consisting of opioid type animals for which the immobilization time was monitored between 12 to 13 pm

The murine behavioural type	Group 1 9-10a.m	Group 2 10-11a.m.	Group 3 11-12a.m.	Group 4 12-13p.m.
A type	92.73± 25.03	113 ± 35.19	126.3 ± 36.6	105.55 ± 28.2
N type	69.55 ± 20.55	79.83 ± 27.42	100.1 ± 21.89	56.27 ± 17.33
O type	91.16 ± 25.26	125.5 ± 44.25	134.6 ±46.7	98.92 ± 28.53

Table 3. The average values of the immobility time (Timob) during FST for the studied behaviour types at different daily hours

Considering the assessment of the chronovariability of the thymic tonus in the adrenergic psychoneuroendocrine type, during FST, it was registered a gradual increase of the immobilization time, during morning hours, continued at noon(12-13 pm), by a significant decrease (figure 4).

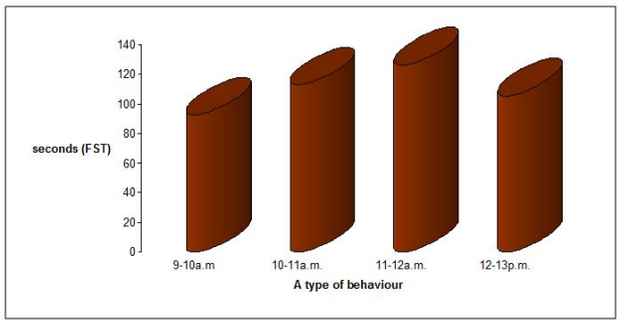

Figure 4. The assessment of the chronovariability of the thymic tonus in the adrenergic psychoneuroendocrine type, during FST

The same pattern was observed for the assessment of the chronovariability of the thymic tonus in the balanced psychoneuroendocrine type, during FST (figure 5).

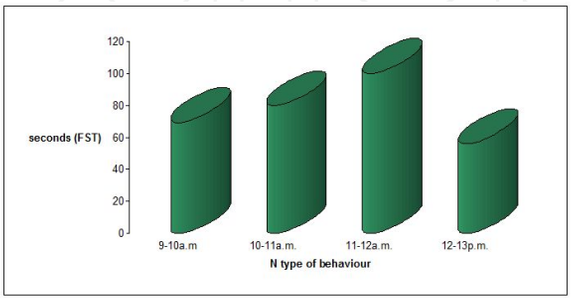

Figure 5. The assessment of the chronovariability of the thymic tonus in the normal psychoneuroendocrine type, during FST

For the opioid psychoneuroendocrine type, it was registered a gradual increase of the immobilization time, at 9-10 am, 10-11 am, 11-12 am, continued at 12-13 pm) by a significant decrease (figure 6).

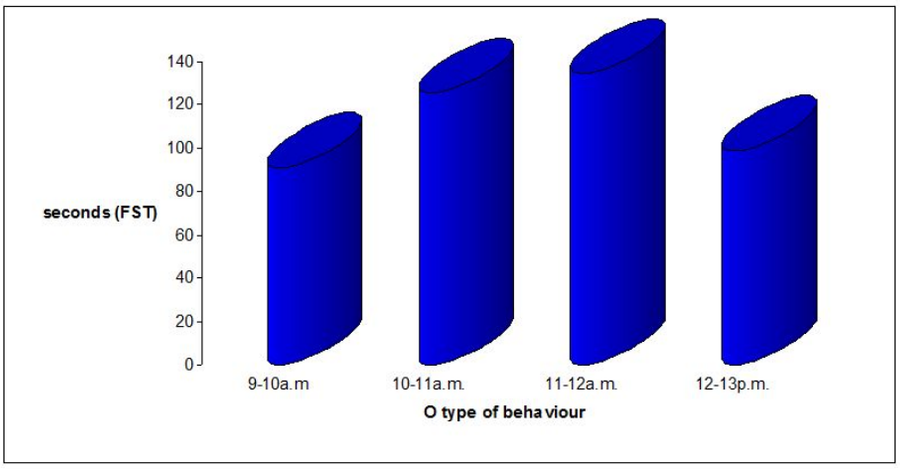

Figure 6. The assessment of the chronovariability of the thymic tonus in the opioid psychoneuroendocrine type, during FST

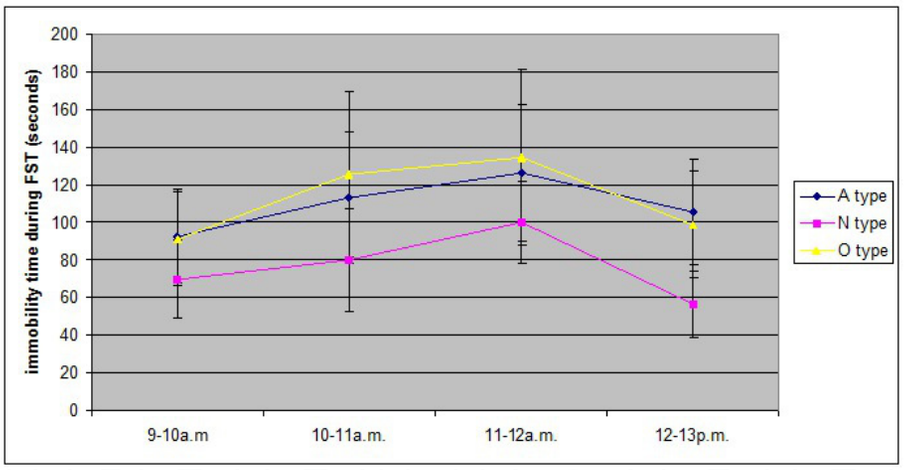

Figure 7. The assessment of the chronovariability of the thymic tonus in the adrenergic, normal and opioid psychoneuroendocrine types, during FST

Analyzing the experimental results obtained, we can highlight some interesting points:

- between 9-10 we have recorded the lowest values of immobilization time (maximum thymic tonus) for all three types of behavior;
- after 10 am (between 10 to 12 am) the values of the immobilization times increase in all cases, so the thymic status involutes towards depression during this time; this behavior is

http://dx.doi.org/10.5772/53323

valid for all psychoneuroendocrine types, becoming statistically significant ($p < 0.05$) in case of the opioid type;

- the peak of "depression" is recorded between 11 to 12 am in all cases and varies as follows: type O (maximum depression - Timob = 134.61 ± 46.70 sec) > TYPE A (Timob = 126.36 ± 36.60 sec) > type N (100.16 ± 21.89 sec);
- after 12 am (between 12 to 13 am) the values of the immobilization times decrease very much, quickly returning to the values recorded at 9 o'clock am (spectacular recursion of the thymic tonus); this issue was highlighted for all psychoneuroendocrine types, indicating that the balanced type distinguished itself significantly from the statistical point of view by the lowest values of the immobilization time (so the most important recursion of the thymic tonus): $p < 0.02$;
- in addition, the values of the immobilization times for the type N (at 12 am) were significantly lower (significantly greater thymic tonus) compared to type A ($p < 0.02$) and to type O ($p < 0.03$) from the statistic point of view.

Viewed through the chronovariability, during the study period, the thymic tonus is dynamic and dependent on the psychoneuroendocrine typology: it decreases gradually for all three psychoneuroendocrine types, between 9-11a.m and signals a "little depression" around the time 11.00 am. Subsequently, the thymic tonus recurs, quite fast, at the values of 9.00 am for all psychoneuroendocrine types under study.

Influence of the behavioural typology on the pharmacological response of some antipsychotic drugs

The experimental study aims the research of the thymic tonus for the three psychoneuroendocrine types after the chronic administration of the following antidepressants:

- imipramine - antidepressant that acts by inhibiting the noradrenaline and serotonin recapture;
- fluoxetine - selective inhibitor of serotonin recapture;
- lithium - normothymic antidepressant (probably) acting by altering the intracellular concentration of inozitoltriphosphate (IP_3).

In order to assess the variability of the antidepressant effect of the imipramine, fluoxetine and lithium carbonate for the three psychoneuroendocrine types, the initial groups of animals corresponding to types A, N and O have been redistributed, as follows:

1. Group 1A: the adrenergic type of animals, which were administrated a dose of 0.1ml/10g body ip normal saline solution in, for 10 days;
2. Group 2A: the adrenergic type of animals, which were administrated a dose of 10mg/kgbw ip imipramine, for 10 days;
3. Group 3A: the adrenergic type of animals, which were administrated a dose of 10mg/kgbw ip fluoxetine, for 10 days;

4. Group 4A: the adrenergic type of animals, which were administrated a dose of 10mg/kgbw ip lithium carbonate, for 10 days;
5. Group 1N: the intermediate type of animals, balanced which were administrated a dose of 0.1ml/10g body ip normal saline solution, for 10 days;
6. Group 2N: the intermediate type of animals, normal, which were administrated a dose of 10mg/kgbw ip imipramine, for 10 days;
7. Group 3N: the intermediate type of animals, which were administrated a dose of 10mg/kgbw ip fluoxetine, for 10 days;
8. Group 4N: the normal type of animals, which were administrated a dose of 10mg/kgbw ip lithium carbonate, for 10 days;
9. Group 1O: the opioid type of animals, which were administrated a dose of 0.1ml/10g body of ip normal saline solution, for 10 days;
10. Group 2O: the opioid type of animals, which were administrated a dose of 10mg/kgbw ip imipramine, for 10 days;
11. Group 3O: the opioid type of animals, which were administrated a dose of 10mg/kgbw ip fluoxetine, for 10 days;
12. Group 4O: the opioid type of animals, which were administrated a dose of 10mg/kgbw ip lithium carbonate, for 10 days.

The research on variability of the antidepressant effect of the three substances studied for the three psychoneuroendocrine types A, N and O was performed using the forced swimming test.

Thus, each animal in each group described above, was subjected to forced swimming in two stages:

- before starting the treatment (Timob1)
- after the administration of the three substances for 10 days (Timob2).

As it can be seen in figure 8, in the case of the adrenergic behavioural type, for all the three antidepressant drugs, after 10 days of treatment, the initial immobilization time decreased, resulting in an obvious antidepressant effect. The most important antidepressant activiy was registered for fluoxetine.

In the case of the normal behavioural type, for all the three antidepressant drugs, after 10 days of treatment, the initial immobilization time decreased, denoting an antidepressant effect. For the balanced psychoneuroendocrine type, the most important antidepressant activiy was registered for imipramine (figure 9).

http://dx.doi.org/10.5772/53323

	Group1		***Group2***		***Group3***		***Group4***	
Murine type	normal saline solution 0.1ml/10 g bw, ip		Imipramin 10mg/kgbw, ip		Fluoxetin 10mg/kgbw, ip		Lithium Carbonate 70mg/kgbw, ip	
	Timob1 (sec)	Timob2 (sec)	Timob1 (sec)	Timob2 (sec)	Timob1 (sec)	Timob2 (sec)	Timob1 (sec)	Timob2 (sec)
A type	M=53.36 ±20.28	M=53.72 ±20.64	M=51.5 ±12.17	M=32.9 ±10.54	(sec)	(sec)	(sec)	(sec)
N type	M=122.45 ±37.25	M=122.95 ±34.55	M=121.5 ±29.34	M=65.45 ±19.48	M=121.82 ±29.19	M=81.13 ±21.69	M=123.78 ±25.20	M=93 ±20.82
O type	M=135.27 ±26.37	M=137.54 ±30.02	M=138.18 ±28.79	M=83.45 ±19.90	M=136.45 ±34.25	M=59.18 ±14.66	M=137.25 ±31.47	M=107.7 ±21.5

Table 4. The average values of the immobility time during FST for the studied behaviour types, before starting the treatment (Timob1) and after the administration of the three substances for 10 days (Timob2).

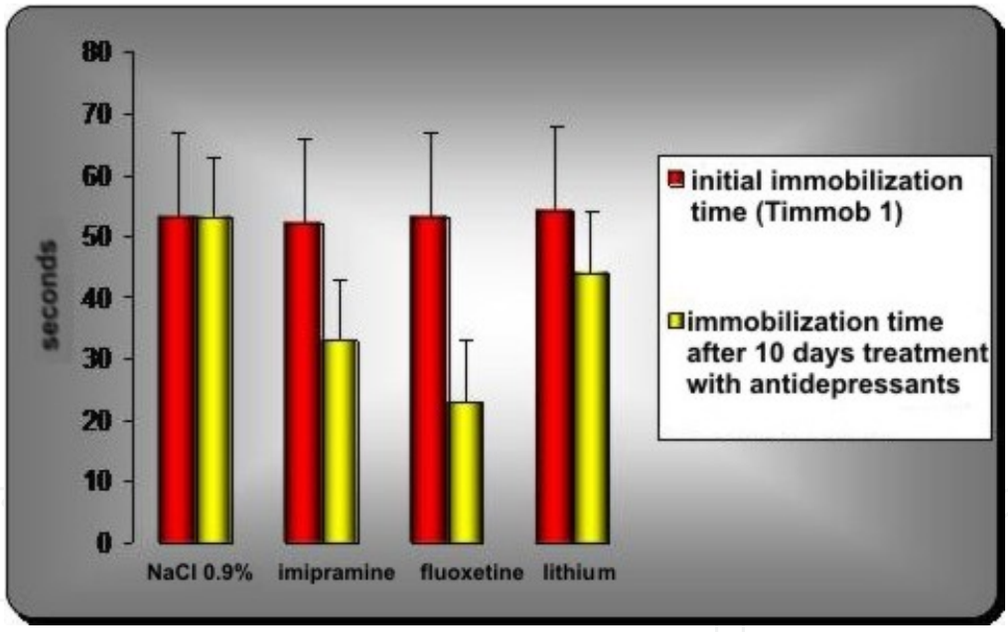

Figure 8. Adrenergic psychoneuroendocrine type. Graphic interpretation of the antidepressant effect of imipramine (10mg/kgbw, ip, for 10 days), of fluoxetine (10mg/kgbw, ip, for 10 days) and of lithium (70mg/kgbw, ip, for 10 ays)

Considering the opioid psychoneuroendocrine type, fluoxetine administered group of animals showed the most important results, decreasing efficiently the initial immobilization time (figure 10).

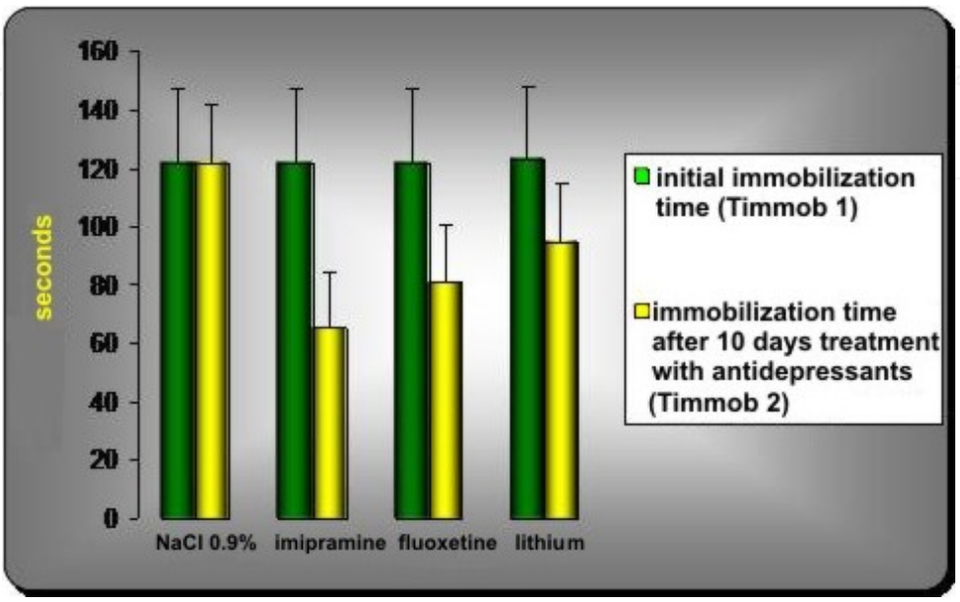

Figure 9. Balanced psychoneuroendocrine type. Graphic interpretation of the antidepressant effect of imipramine (10mg/kgbw, ip, for 10 days), of fluoxetine (10mg/kgbw, ip, for 10 days) and of lithium (70mg/kgbw, ip, for 10 days)

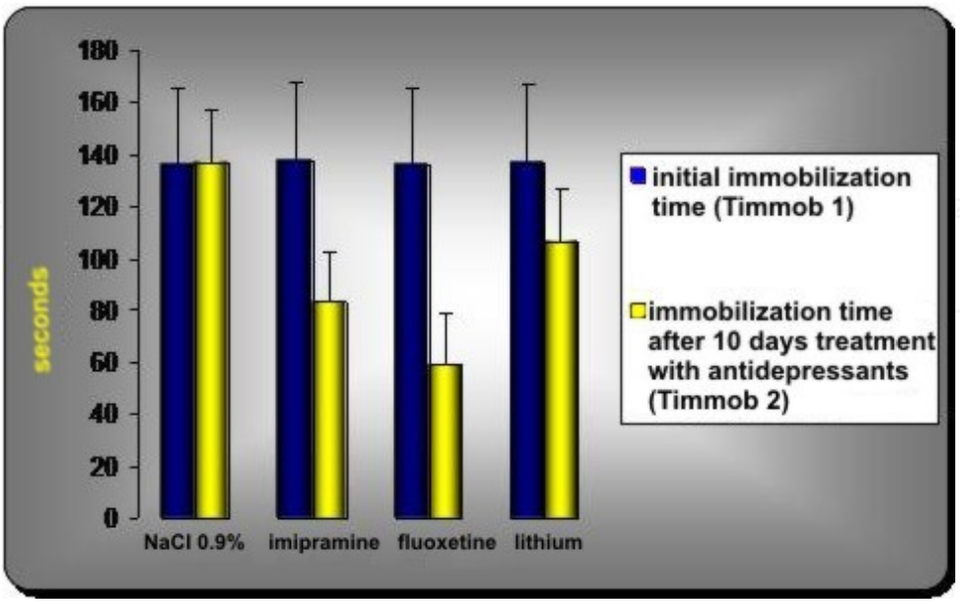

Figure 10. Opioid psychoneuroendocrine type. Graphic interpretation of the antidepressant effect of imipramine (10mg/kgbw, ip for 10 days), of fluoxetine (10mg/kgbw, ip for 10 days) and of lithium (70mg/kgbw, ip for 10 days)

http://dx.doi.org/10.5772/53323

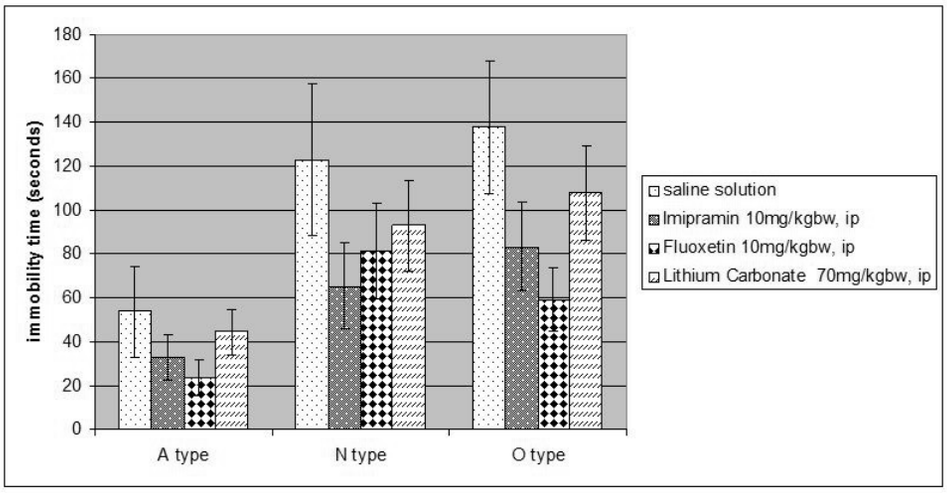

Figure 11. Graphic interpretation of the antidepressant effect of imipramine (10mg/kgbw, ip for 10 days), of fluoxetine (10mg/kgbw, ip for 10 days) and of lithium (70mg/kgbw, ip for 10 days) for the three psychoneuroendocrine types

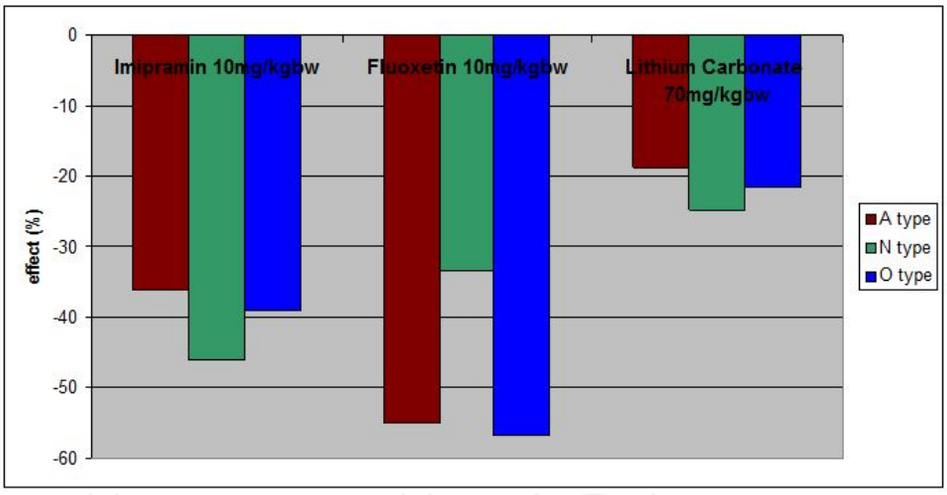

Figure 12. The percentual effect of imipramine, fluoxetine and lithium on murine behaviour in the FST

(Timob after 10 days of antidepressants treatment vs. Timob at the beginning of the experiment)

The effects of imipramine, fluoxetine and lithium on murine behaviour in the FST are shown in figure 12 and 13.

Analyzing the experimental results, we can highlight the following observations:

- in the case of the adrenergic psychoneuroendocrine type, the intensity of the antidepressant effect of the medications administrated (the effect varies inversely with the values of the immobilization times recorded through the "desperation" test) varies in the following

order: fluoxetine (Timob = 23.8 ± 7.98sec) > imipramine (Timob = 32.9 ± 10.54sec) > lithium (Timob = 44.5 ± 10.4sec) (Fig. 12);

- in case of the normal, balanced psychoneuroendocrine type, the antidepressant effect of the medications administrated varies in the following order imipramine (Timob = 65.45 ± 19.48sec) > fluoxetine (Timob = 81.13 ± 21.69sec) > lithium (Timob = 93 ± 20.82sec);
- in case of the opioid psychoneuroendocrine type the antidepressant effect of the medications administrated varies in the same order as in type A, namely fluoxetine (Timob = 59.18 ± 14.66sec) > imipramine (Timob = 83.45 ± 19.90sec) > lithium (107.7 ± 21.5sec).

Fluoxetine developed the most important antidepressant effect, mostly in the extreme typologies:

- A type:
- 54.92% (Timob2 vs. Timob1, namely immobility time after 10 days of fluoxetine vs. immobility time at the beginning of the experiment);
- 55.69% (Timob2 vs. saline solution);
- O type:
- 56.62% (Timob2 vs. Timob1)
- 56.97% (Timob2 vs. saline solution).

On the other the intermediated, equilibrated N type was highly reactive to imipramine:

- 46.13% (Timob2 vs. Timob1)
- 46.76% (Timob2 vs. saline solution).

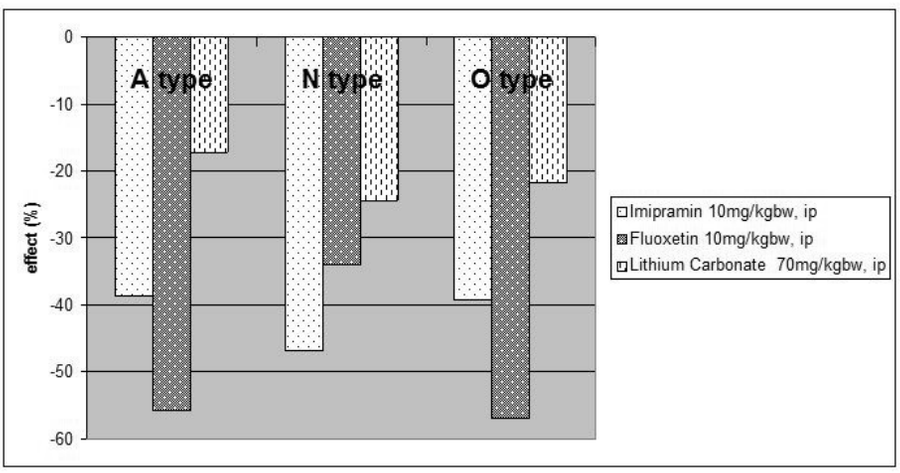

Figure 13. The percentual effect of imipramine, fluoxetine and lithium on the three psychoneuroendocrine types in the FST (Timob after 10 days of antidepressants treatment vs. saline solution)

Some interesting findings were revealed by the statistical analysis of the experimental data. Thus, the statistical comparison between the groups treated with the same antidepressant

http://dx.doi.org/10.5772/53323

but coming from different typologies (e.g. Group A and Group O treated with fluoxetine) provided biological significance in all cases.

The statistical analysis of the results from the same psychoneuroendocrine typology but between groups of animals treated with various agents (e.g. Group O treated with imipramine and Group O treated with lithium) gave the biological significance in all cases except for the adrenergic type. In this case, the antidepressant effect of the different medications was statistically different only for Group A imipramine / and Group A lithium ($p < 0.05$).

6. Conclusions

All experimental observations presented support the theory of the pharmacological variability, as a manifestation of the biological variability imprinted by the psychoneuroendocrine typology. From this point of view, for an optimal pharmacological effect of antidepressant medications, one should take into consideration the following aspects:

- the adrenergic psychoneuroendocrine type has a very good general, basal thymic tonus;
- the opioid psychoneuroendocrine type has a low basal thymic tonus;
- the dynamics of thymic state is optimal, regardless of the psychoneuroendocrine typology, between 9-10 a.m. and 12-13 a.m.;
- there is a peak of "depression" daily, between 11-12 a.m., for all types of behavior;

From the antidepressant medication investigated, the extreme behavioural typologies (adrenergic and opioid types) have proven to be extremely responsive to the selective inhibitors of the serotonin recapture (as fluoxetine), while the balanced type reacted optimally to the group of nonselective inhibitors of the noradrenaline and serotonin recapture (as imipramine). These findings may be interestingly correlated with our previous reports regarding the monoaminergic status of the behavioural murine types. In this regard, we showed that the A and O types develop low amounts of serotonin and, therefore, become sensitive against antidepressants that selectively inhibit serotonin reuptake (like fluoxetine) [2].

Lithium, a controversial and incompletely elucidated antidepressant in terms of the action mechanisms, but with indication of choice in maniac-depressive syndrome, has proven the lowest effect in the case of the adrenergic psychoneuroendocrine type, but significant results in the intermediate type. Furthermore the study showed that extreme behavioural typologies are not suitable for lithium treatment.

A proper individualized neuropsychopharmacotherapy is submitted to many variables, like genetic and molecular status, and the behavioural typology seems to be important to be considered.

Author details

Andreea Letitia Arsene*, Niculina Mitrea, Dumitru Lupuliasa, Cristina Manuela Dragoi, Alina Crenguta Nicolae, Ion-Bogdan Dumitrescu, Dragos Florian Ciolan and Doina Draganescu

*Address all correspondence to: andreeanitulescu@hotmail.com

University of Medicine and Pharmacy "Carol Davila", Faculty of Pharmacy, Bucharest, Romania

References

[1] Appleton, K. M., et al. (2007). Type A behaviour and consumption of atherogenic diet: No association in the PRIME study. *Appetite*, 46.

[2] Arsene, A. L. (2011). Bipolar Disorder- A Portrait of a Complex Mood Disorder. *Rijeka: InTech*.

[3] Benfey, B. G., et al. (2001). Evaluation of sympathetic beta-receptor blockade by recording the rate of ventricular pressure rise in cats. *Br. J. Pharmacol*, 30, 23-29.

[4] Bergquist, J., et al. (2002). Catecholamines and methods for their identification and quantitation in biological tissue and fluids. *Journal of Neuroscience Methods*, 113, 1-13.

[5] Brian, Koehler. (2005). Bipolar Disorder, Stress, and the HPA Axis. Available from. http://www.isps-us.org/koehler/bipolar_stress.htm.

[6] Carolina-Rubalcava, López. (2012). Effects of Antidepressants. *Rijeka: InTech*.

[7] Cristea, A., et al. (1997). The nervous behaviour of the adrenergic and opioid types during several pharmacologic tests. *Farmacia*, 45(2), 71-79.

[8] Cristea, A., et al. (1994). The evolution of the painful sensitivity in acute and chronic stress. Rom. J. Phisyol. , 31(1-4), 75-79.

[9] De Nayer, A., et al. (2002). Venlafaxine compared with fluoxetine in outpatients with depression and concomitant anxiety. *The International Journal of Neuropsychopharmacology*, 5(2), 115-120, 1461-1457.

[10] Duffield, G. E., et al. (2002). Programs of transcriptional activation, signaling and protein turnover revealed by microarray analysis of mammalian cells. *Curr. Biol*, 12, 551-557.

[11] Eduardo, Vignoto. Fernandes. (2012). Effects of Antidepressants. *Rijeka: InTech*.

[12] Hache, G., et al. (2012). Antinociceptive effects of fluoxetine in a mouse model of anxiety/depression. *Neuroreport*, 23(9), 525-529.

[13] Haynes, S. G., et al. (1978). The relationship of psychosocial factors to coronary heart disease in the Framingham Study: Methods and risk factors. *Am.J.Epidemiol.*, 107.

[14] Herman, S., et al. (1981). Self ratings of type A (coronary prone) adults. *Psychosom. Med.*, 43(5), 405-413.

[15] Ipek, Komsuoglu. Celikyurt. (2012). Effects of Antidepressants. *Rijeka: InTech*.

[16] Jones, K. V. (1985). The thriel of victory: blood pressure, variability and type A behavior pattern. *J.Behav.Med.*, 8(3), 277-285.

[17] Le Melledo, J. M., et al. (2001). The influence of Type A behavior pattern on the response to the panicogenic agent CCK-4. *J. Psychosom. Res.*, 51.

[18] Masse, F., et al. (2005). M.α2-adrenergic agonistas antagonise the anxiolytic-effect of antidepressants in the four-plate test in mice. *Behav. Brain Research*, 52, 174-176.

[19] Meesters, C. M. G., & Smulders, J. (1994). Hostility and myocardial infarction in men. *Journal of Psychosomatic Research*, 38(7), 727-734.

[20] Nascimento, et.al. . (2005). Pilocarpine induced status epilepticus:Monoamine level, muscarinic and dopaminergic receptors alterations in striatum of young rats. *Neuroscience Letters*, 383, 165-170.

[21] Oedegaard, K. J., et al. (2006). Type A behaviour differentiates bipolar II from unipolar depressed patients. *J.Behav.Pharmacol.*, 90.

[22] Ortiz, J. G., et al. (2000). Plasticity of excitatory amino acid transporters in experimental epilepsy. *Epilepsia*, 41, 104-110.

[23] Owens, M., et al. (2008). Estimates of serotonin and norepinephrine transporter inhibition in depressed patients treated with paroxetine or venlafaxine. Neuropsychopharmacology 0089-3133X, 33(13), 3201-3212.

[24] Pacher, P., et al. (2001). Furst S.Serotonin Reuptake Inhibitors Fluoxetine And Citalopram Relax Intestinal Smooth Muscle. *Can.J.Physiol.Pharmacol*, 79, 580-584.

[25] Papakostas, G., et al. (2008). A meta-analysis of clinical trials comparing mirtazapine with selective serotonin reuptake inhibitors for the treatment of major depressive disorder. *Journal of Psychopharmacology*, 22(8), 843-848, 0269-8811.

[26] Petit-Demouliere, B., Chenu, F., & Bourin, M. (2005). Forced swimming test in mice: a review of antidepressant activity. *Psychopharmacology Berl*, 177(3), 245-255.

[27] Powell, L. H., et al. (1984). Can type A behavior be altered after myocardial infarction? A second year report from the Recurreent Coronary Prevention Project. *Psychosom. Med.*, 46.

[28] Rainer, Q., & Et, al. (2012). Functional status of somatodendritic serotonin 1A autoreceptor after long-term treatment with fluoxetine in a mouse model of anxiety/depression based on repeated corticosterone administration. *Molecular pharmacology*, 81(2), 106-112.

[29] Rhodewalt, F. (1984). Self involvment, self attribution and type A coronary-prone behavior pattern. *J.Pers.Soc.Psychol*, 47(3), 662-670.

[30] Rosenman, R. H. (1978). The Interwiew method of assessment of the coronary prone behavior pattern. *Dembronski, T.M., et al. eds., Coronary prone behavior, New York*, 55-70.

[31] Serretti, A., & Mandelli, L. (2008). The genetics of bipolar disorder: genome 'hot regions,' genes, new potential candidates and future directions. *Molecular Psychiatry*, 13(8), 742-771.

[32] Silvana, da Silva. (2012). Effects of Antidepressants. *Rijeka: InTech*.