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Comparative study of neuroprotective effect of tricyclics *vs.* trazodone on animal model of depressive disorder

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Abstract

The neurobiological model of depressive disorder may be correlated with the animal model on rat, hyperactivity of the hypothalamic–pituitary–adrenal (HPA) axis, the increase of cortisol level being specific to the model of depression in women. The neurobiological model of depression in women presents vulnerabilities for some cerebral structures (hippocampus, frontal cortex, cerebral amygdala). A decrease of frontal cortex and hippocampus volumes are recognized in depressive disorder in women, depending on duration of disease and antidepressant therapy. Neurobiological vulnerability may be pronounced through cholinergic blockade. The purpose of the study was to highlight the cytoarchitectural changes in the frontal cortex and hippocampus by comparing two antidepressant substances: amitriptyline with a strong anticholinergic effect and trazodone, without anticholinergic effect. The superior neuroprotective qualities of trazodone for the frontal cortex, hippocampus and dentate gyrus are revealed. The particular neurobiological vulnerability of depression in women requires a differentiated therapeutic approach, avoiding the use of antidepressants with anticholinergic action.

***Keywords*:** neuroprotection, cholinergic blockade, antidepressants, hippocampus, frontal cortex.

Introduction

The neurobiological model of depressive disorder highlights the involvement of affective-emotional structures (cerebral amygdala and limbic system) in the interconnection with the cognitive structures (hippocampus, frontal cortex). The neurobiochemical mechanisms in depression in women highlight the potentiation of neuromediator deficits by hypothalamic–pituitary–adrenal (HPA) axis hyperactivity with high levels of cortisol and a major vulnerability in women to stress.

Elevated levels of plasma cortisol [1] and deficits in declarative memory are mediated by the hippocampus [2]. Preclinical studies have confirmed that chronic psychosocial stress and cortisol administration inhibit neurogenesis in the dentate gyrus [3] and cause atrophy or remodeling of the apical dendrites of the pyramidal neurons in the CA3 region of the hippocampus [4].

A smaller hippocampal volume in adult women with major depressive disorder was observed exclusively in women with a positive history for severe and prolonged physical psychological abuse in childhood [5]. Women reported more interpersonal changes whereas men reported more legal and work-related stressful life events. Most life event categories influenced the risk for major depression similarly in the two genders. The greater prevalence of major depression in women *vs.* men is due neither to differences in the rates of reported stressful life events nor to differential sensitivity to their pathogenic effect [6].

We can discuss about some neurobiological particularities of depression in women, in direct connection with high level of cortisol and hyperactivity of HPA axis: loss of hippocampal volume, hypercortisolemia, early installed cognitive deficit, decrease of cerebral amygdala volume and vulnerability of prefrontal cortex for the development of atrophy.

High levels of cortisol in the major depressive disorder may cause several alterations of the hippocampus, including CA1/CA3 area and cingulate and entorhinal cortex. The hippocampal lesions may be responsible for the cognitive impairment, which could be aggravated by the cholinergic blockade [7]. While tricyclics show a significant anticholinergic action, trazodone has virtually no such effect. Our study aims to highlight the differences between the two classes of antidepressants regarding their potential of neurobiological aggressiveness.

Materials and Methods

We formed four groups of 20 adults Wistar rats each, weighing 200–250 g, held during the study in the same temperature, humidity, food and ambient stress-less conditions: N1 – control group; N2 – received

dexamethasone with subsequent increase of cortisol levels; N3 – was administered dexamethasone and amitriptyline; N4 – was administered dexamethasone and trazodone.

The studied substances were given in intraperitoneal administration, daily, for 14 days, saline solution equivalent to: dexamethasone (0.20 mg/kg/day), amitriptyline (0.5 mg/kg/day), and trazodone (0.20 mg/kg/day).

The rats were sacrificed in the 14th day, at six hours after the last substance administration. The sampled brain (hippocampus and frontal cortex) was histopathologically processed: formalin (10%) fixation, ethanol (96%) dehydration and paraffin embedding. Microtome sections were stained using Hematoxylin–Eosin, Goldner's trichrome, PAS-Hematoxylin, Toluidine Blue, Methylene Blue for Nissl bodies and argentic impregnation for neurofibrils. The sections obtained were examined in light microscopy. The purpose was to highlight the cytoarchitectural changes in the frontal cortex and hippocampus in all four groups and to identifying different neuroprotective effects.

Results

Hypercortisolemia causes structural changes in the frontal cortex and hippocampus of rats involved in our study.

In the frontal cortex, compared with the control group, after administration of dexamethasone, significant cytoarchitectural changes confirming the aggressiveness of cortisol by cytotoxic mechanisms are observed (Figure 1).

It must be noted that in the frontal cortex of rats, after administration of dexamethasone, a serious deterioration of neurons predominantly in layers I and II with pinocytosis was seen.

At the hippocampal level compared with the control group, dexamethasone causes a loss of structure in the CA1–CA3 area, with multiple vacuolization, neural loss and significant changes to the neuropil (Figure 2).

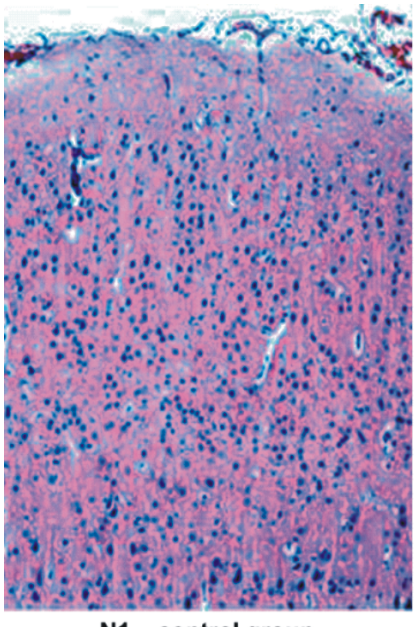
Dexamethasone produces significant changes in the dentate gyrus, with altering of neural connections, neural massive destruction and important vacuolization, with a migrating trend of destroyed neuronal bodies in the supporting area of the white substance (Figure 3).

Tricyclic antidepressants in association with dexamethasone cause deterioration and changes of neural structures in the frontal cortex and hippocampus of rats, compared with a reduced effect of dexamethasone administered with trazodone. The aggressive effect of amitriptyline with significantly reduced neuroprotection may be linked to the strong anticholinergic action of this substance, trazodone being devoid of anticholinergic effects.

In the frontal cortex, dexamethasone associated with amitriptyline emphasizes the neuronal loss in layers I, II and III respectively, and amplifies the vacuolar-type mechanisms. Association of trazodone shall prove to the rat his superior neuroprotective efficiency by keeping the majority of neural structures, the only change being represented by the presence of vacuolizations in the neuropil (Figure 4).

In N3 subjects, the hippocampal lesions were far more prominent, affecting the neuron number, while group N4 showed minimal lesions. Subjects of N3 showed intense vacuolization in the white substance (Figure 5).

The cytoarchitectural abnormal changes in the dentate gyrus are much more pronounced for the group with dexamethasone and amitriptyline (Figure 6).



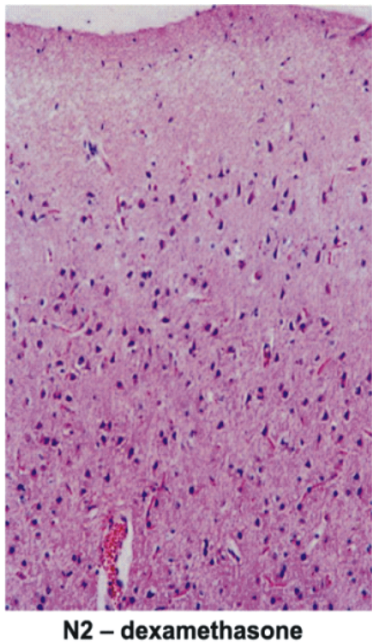
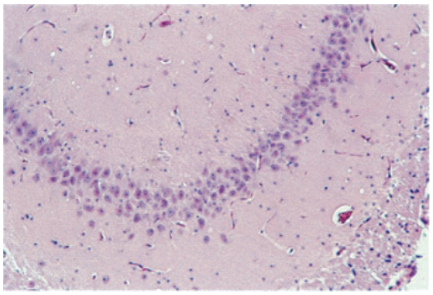


Figure 1 – ***Cytoarchitectural changes in the frontal cortex of rats after dexamethasone administration.***



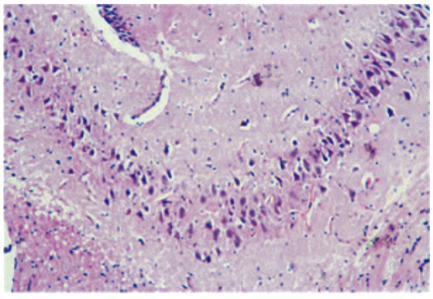
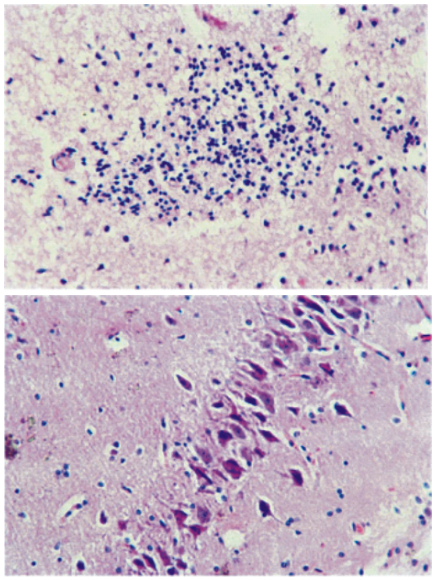
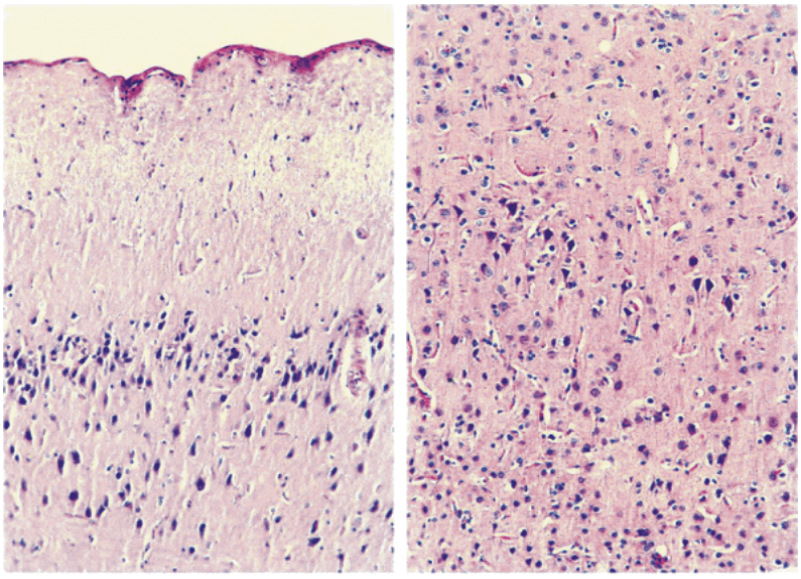


Figure 2 – ***Cytoarchitectural changes in the hippocampus of rats after dexamethasone administration.***



N2 – dexamethasone

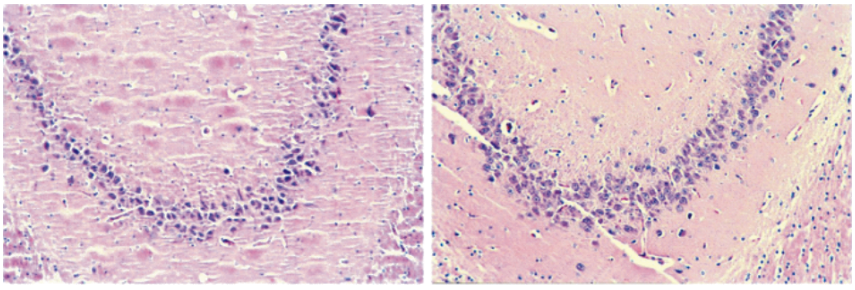
Figure 3 – ***Cytoarchitectural changes in the dentate gyrus of rats after dexamethasone administration.***



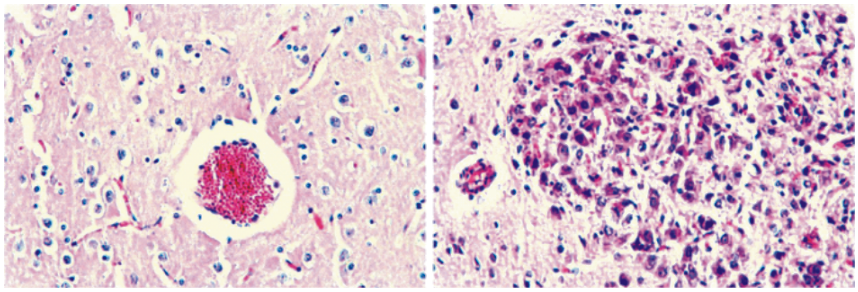
N3 – dexamethasone and amitriptyline N4 – dexamethasone and trazodone

Figure 4 – ***Changes in the structure of the frontal cortex in rats after administration of dexamethasone with amitriptyline (N3) compared with dexamethasone and trazodone (N4).***

Figure 5 – ***Changes in the structure of the hippocampus in rats after administration of dexamethasone with amitriptyline (N3) compared with dexamethasone and trazodone (N4).***



N3 - dexamethasone and amitriptyline N4 - dexamethasone and trazodone



N3 - dexamethasone and amitriptyline N4 - dexamethasone and trazodone

Figure 6 – ***Changes in the structure of the dentate gyrus in rats after administration of dexamethasone with amitriptyline (N3) compared with dexamethasone and trazodone (N4).***

Discussion

Dexamethasone is a much-used glucocorticoid in various pathological conditions due to the reduction of inflammatory processes and its immunosuppressive properties. Many authors have reported the development of various psychiatric disorders such as psychotic disorders, mood disorders, anxiety, delirium, etc., following corticosteroid therapy [8]. In humans, the effects of large doses or prolonged glucocorticoid therapy on nerve cells are less known or studied. Most data come from experimental studies. Thus, Barrichello T *et al.* [9] found an alteration of proteins in the hippocampus and cerebral cortex in rats with pneumonia treated with dexamethasone compared to controls, and Leib SL *et al.* [10] have shown that dexamethasone enhances neuronal apoptosis in the hippocampus and reduces learning capacity.

In our study, there was a marked reduction in the number of neurons in the frontal brain and hippocampus after administration of dexamethasone in high concentrations combined or not with amitriptyline and the neuroprotective effect of trazodone. The most affected neurons were those in the superficial layers of the cortex, where neuronal loss resulted in a spongy appearance of the area. Neuronal depletion was associated with neuronal changes such as pyknosis, karyorexis and neuronal cell type pyknosis, karyorexis or karyolysis, changes that precede cell death.

The animal model (rat) of depressive disorder demonstrates the significant decrease of neuroprotection caused by hypercortisolemia and the aggressiveness of endogenous cortisol on the frontal cortex and hippocampal structures, confirming the existing data in the literature, which mentions in a meta-analysis the existence of frontal cortex atrophy [11] and the decrease

in hippocampal volume [12]. Changes to the frontal cortex and hippocampal structures may be exacerbated by the long duration of disease without treatment and intensive psycho-stress factors [13].

Lately, the intimate mechanisms of corticosteroid action on the nervous system began to be deciphered. Thus, Johnson S *et al.* [14] indicate that corticosteroids play an important role in neuronal death and depression. Important amounts of glucocorticoids are produced in the body in a state of stress when the adrenal gland is required to secrete these hormones in excess. Also, large amounts of glucocorticoids may result from anti-inflammatory or immunomodulatory treatments. However, an abnormal increase in glucocorticoid levels was associated with hippocampal atrophy [15] and major depression [16].

Dexamethasone increases the activity of monoamine oxidases (MAO) A and B, both in neuronal cells [17] and astrocytes, and reduces the number of viable cells in the brain [18]. Elevated MAO levels degrade serotonin and produce reactive oxygen species (ROS) such as hydrogen peroxide, which can cause nerve cell death [19].

We believe that in patients undergoing prolonged glucocorticoid therapy in large quantity active neuroprotection neuronal is required to prevent neuronal lesions and installation of psychiatric disorders.

Conclusions

The anticholinergic effect induced by tricyclic antidepressants combined with high levels of cortisol constitutes an important risk factor for the alteration of hippocampal and frontal structures, while trazodone is maintaining the integrity of these structures. The particular neurobiological vulnerability of depression in women requires a differentiated therapeutic approach, avoiding the use of antidepressants with anticholinergic action.

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