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Nuclear features of depression. A medical model of the depressive disease

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NEURAL TRANSMISSION MALFUNCTION IN THE DEPRESSIVE DISEASE

The present article is a résumé. It deals about the practice of describing depression as a medical disease, in making correlation between the findings of a brain chemical malfunction and the nuclear features of depression. By «nuclear» features we will mean the symptoms for which a correlation with some kind of chemical malfunction has been established, allowing the understanding of the classical symptomatology described as representative of depression from them. The author is conscious of having adopted some scientific «licenses» in order to give consistency to the set.

Using different research procedures, ranging from the study of the receptors through the levels of amines and their metabolites in various fluids, to the indirect use of neuroendocrine probes, an aminergic hypoactivity in this disease has been established. Indeed, repeated evidences indicate that the main thing in order to understand the biochemical changes that underlie depression is the fact that at least two classical neurotransmitters are involved, being one an indolamine: serotonin or 5-hydroxytriptamine (5HT), and the other a catecholamine: noradrenaline (NA) (Coppen, 1967, 1972; Sarrias et al., 1987, 1991; García Sevilla et al., 2004; Delgado et al., 1999).

NUCLEAR FEATURES OF DEPRESSION ACCORDING TO THE AMINERGIC MALFUNCTION

The aforementioned aminergic malfunction can be related to the depressive symptomatology if we take as nuclear features of depression the immediate outcomes of a reduction of the serotoninergic activity and of the noradrenergic activity.

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5HT malfunction is basically related to a low stress tolerance and to a reduced pain threshold, and the circadian cycles disorder in which the activity of another indolamine, such as melatonin, is essential, is partly also related. Catecholaminergic hypofunction will result in cognitive malfunction, body hypoactivity and in a troubled sensing for pleasant feelings.

DECREASED STRESS TOLERANCE

This phenomenon is probably the touchstone in order to understand the appearance of depressive features in sustained stress situations, the extremely low stress tolerance showed by depression patients, and some hypothetical connections between the symptoms of depression and of anxiety.

The serotoninergic system is the main neuroadapter. The appearance of a stressor in the environment calls for a greater serotoninergic neuromodulative activity over the remainder neurotransmission systems, whose activity will increase. If the «urge» is over the «endowment», depressive features can appear. This is similar to what happens with a patient having a primary serotoninergic malfunction.

Of essential interest for that purpose are the studies about the anhedonical model taken as an experimental model of depression. This experimental design makes a register of two kinds of animal activity: the pro-social conduct and the number of times that the animal spends water with sucrose from the dispenser. Afterwards, the animal undergoes minor stress situations, such as tilting the cage, soaking the floor, hindering sleep, and so on. This context would mean mild or moderate stress situations of daily life in humans. The next behavior register displays a radical and significant reduction in the consumption of sweetened water, so as of the pro-social conduct, showing an anhedonical behavior. The experiment is repeated subsequently in animals that have received a previous treatment with antidepressive drugs. A very quick restoration of the anhedonical behavior will appear; even the possibility that this conduct could be avoided does exist (Sánchez et al., 2000).

REDUCED PAIN THRESHOLD

In classical descriptions of the depressive disease, concepts such as «somatization», «hypochondriacal symptoms», or «body projections» are portrayed as representative. Somatic complaints are indeed one of the commonest features in depressive patients. However, a neurochemical basis does exist, and allows the understanding of their pathogenesis if we are grounded on the medical model. Their improvement with the antidepressive treatment is understandable likewise.

The involvement of the very same neurotransmitters for the control of the noniceptive tolerance and of the depression pathogenesis suggests that the aforementioned aminergic malfunction causes both kinds of features. As a matter of fact, low tolerance to somatic complaints is one of the nuclear features of depression, afar from sophisticated psychological of phenomenological suppositions.

Most authors that are working in the field of pain control think of the downward projections in the raphe dorsal nucleus as a serotoninergic pathway, and of the downward projections in the locus ceruleus as a noradrenergic pathway. These two are the main modulating pathways for noniceptive feelings. The upward projections of both are related to the appearance of depressive states. Their integrity and their balance are necessary for having an adequate tolerance to pain (Micó et al., 2003). Thus, it is not surprising that in such an illness as is depression the pain threshold could be reduced, and the perception of the somatic complaints could be increased.

Dual agonist antidepressive drugs 5HT/NA, such as duloxetin, show a specific activity and improve the somatic complaints in patients with depression (Nelson et al., 2005).

COGNITIVE MALFUNCTION IN DEPRESSION

Almost all patients that experience a depressive episode show a significant cognitive malfunction. As a matter of fact, according to the DSM-IV (American Psychiatry Association, 1994), the group of features for cognitive malfunction holds by his own right the full item 8 of range A criteria in the diagnosis of a depressive episode. Usually, the commonest cognitive changes in the depressed patient are related to inhibition, to a drastic failure in the processing and carrying-out speed for tasks, so as of the speed and extent of language in serious cases. In a study about control of the cognitive function and activation needs using neuroimaging, larger activation needs of the brain specific circuits to control the cognitive function in general, and the work memory in particular, were proved in depressive patients (Harvey et al., 2005).

Cognitive malfunction in depression is usually quite well recovered. If it persists, a thorough differential diagnosis with dementia shall be done, since only cases that appear in a co-morbid way with neurodegenerative diseases show cognitive malfunction as time goes by (Ganguli et al., 2006).

The NA system plays an essential role, since it acts as an interphase between the external world and the cognitive processing of the stimuli coming from it. Thus, the role that this system plays over alert, attention, memory and learning is obviously outstanding (Jouvet et al., 1991).

The use of drugs that enhance NA transmission causes a significant improvement of the reference learning. In particular atipamazol, an antagonist of _2 pre-synaptical adrenoreceptors, and therefore a blocker of the negative feedback mechanism in the synapse, is a drug that improves the learning, the short-term memory, and the information processing speed thanks to the stimulation of the NA activity (Haapalinna et al., 1998).

On the other hand, one of the commonest causes of bad cognitive performance in depression is a disturbed attention. Studies in primates and human volunteers show the importance of the NA pathways in the dorsal bundle of the LC for lowering the inattention caused by irrelevant stimuli (Coull, 1994). These studies explain the as much unknown as outstanding role of NA in the cognitive function and the importance of its integrity in the maintenance of a cognitive function acceptable as a whole.

DISORDER OF THE CIRCADIAN CYCLES: SLEEP ARCHITECTURE

Most patients with depression experience sleeping disorders. Many authors have established very close relationships between mood and sleep control, whether in patients or in healthy controls. As a matter of fact, depressed patients experience disorders of the circadian cycles, such as changes of temperature and cortisol levels all day long. However, there is no doubt that, from a psychopathological point of view, the most significant disturbance lies in the structure or architecture of the sleep. Depressed patients complaint about a bad sleep performance, even if the number of sleep hours remains unchanged.

Changes appeared in polysomnographical registers include a shortened REM latency, what means that the first NREM phase, which is the deeper dreaming phase and a clue for the sleep efficiency, is very short or non-existent. The patients show also an increased REM density. These changes can even go before the depressive episode, and be the main complaint of the patient (Ohayon and Roth, 2003). Its persistence worsens the depression prognosis as for the risk of recurrence and/or relapse refers (Lustberg and Reynolds, 2000).

Thanks to the pharmacological treatment, the serious disturbance of the sleep efficiency returns to normal in a

Table 1 Chemical changes in depression. Possible outcomes and correlations with the conventionally described symptomatology

Chemical change	Nuclear feature	Repercussion	Features
5HT hypofunction			
Serotonin	Low pain resistance	Usual body complaints: headache, backache, abdominal distention... are «experience» in an amplified and unbearable way	Somatizations Hypochondrial features
	Low stress resistance	Everything is found difficult and complex; unable to take a decision, «everything turns into a mountain». Intense and non-modifiable anxiety, interference with general performance Hopelessness in front of conventional situation	Pessimism in front in the future Anxiety Sorrow Self-blaming
Melatonin	Circadian rhythms disorders (sleep and its structure, cortisol and temperature)	Shortened REM latency, increased REM density, reduced slow (deep) dreaming: low sleep efficiency Disturbed corticol cycle	Insomnia, early awakening, non-resting feeling. Hypersomnia. Morning worsening (daily changes)
Catecholaminergic hypofunction			
Dopamin	Troubled sensing for pleasant feelings	Lack of positive reinforcement with progressive loss of familial, working, enjoying and sexual interests. Progressive lack of interest in life. Anorexia	Lack of interest in keeping him/herself alive, death ideas. Self-esteem devaluation, self-blaming ideas. Self-image devaluation, ruin ideas
Noradrenalin	Low general activation of the CNS Cognitive malfunction	General lack of vitality feeling. Inadequate activation of CNS. Reduced attention, self-absorption, and activation	Inhibition, tiredness, weariness, limb heaviness. Complaint concerning intellectual performance

significant quick way, and this essential component of the circadian rhythms will be restored.

CLINICAL-PATHOLOGICAL CORRELATION: THE DEPRESSIVE EPISODE

To end, and as a conclusion, the following table is an attempt to connect the described biochemical bases with their immediate outcomes and, in turn, to the depressive symptomatology portrayed by the patient along the psychopathological examination.

REFERENCES

American Psychiatry Association. Diagnostic and Statistical Manual of Mental Disorders. American Psychiatry Press. Washington, 1994.

Coppen A. The biochemistry of affective disorders. Br J Psychiatry 1967;113:1237-64.

Coppen A. Indoleamines and affective disorders. J Psychiatr Res 1972; 9:163-71.

Coull JT. Pharmacological manipulations of the alpha 2-noradrenergic system. Effects on cognition. Drugs Aging 1994;5:116-26.

Delgado PL, Miller HL, Salomon RM, Licinio J, Krystal JH, Moreno FA, et al. Tryptophan-depletion challenge in depressed patients treated with desipramine or fluoxetine: implications for the role of serotonin in the mechanism of antidepressant action. Biol Psychiatry 1999;46:212-20.

Ganguli M, Du Y, Dodge HH, Ratcliff GG, Chang CC. Depressive symptoms and cognitive decline in late life: a prospective epidemiological study. Arch Gen Psychiatry 2006;63:153-60.

Garcia-Sevilla JA, Ventayol P, Pérez V, Rubovszky G, Puigdemont D, Ferrer-Alcon M, et al. Regulation of platelet alpha 2A-adrenoceptors, Gi proteins and receptor kinases in major depression: effects of mirtazapine treatment. Neuropsychopharmacology 2004;29:580-8.

Haapalinna A, Sirvio J, Lammintausta R. Facilitation of cognitive functions by a specific alpha2-adrenoceptor antagonist, atipamezole. Eur J Pharmacol 1998;347:29-40.

Harvey PO, Fossati P, Pochon JB, Levy R, Lebastard G, Lehericy S, et al. Cognitive control and brain resources in major depression: an fMRI study using the n-back task. Neuroimage 2005;26: 860-9.

Jouvet M, Albarede JL, Lubin S, Meyrignac C. Noradrenaline et vieillissement cerebral. Encephale 1991;17:187-95.

Lustberg L, Reynolds CF. Depression and insomnia: questions of cause and effect. Sleep Med Rev 2000;4:253-62.

Micó JA, Rojas-Corrales MO, Holgado MA. The pathophysiology of pain in depression. Eur Neuropsychopharmacol 2003;13(Suppl. 4): 98-9.

Nelson JC, Wohlreich MM, Mallinckrodt CH, Detke MJ, Watkin JG, Kennedy JS. Duloxetine for the treatment of major depressive disorder in older patients. Am J Geriatr Psychiatry 2005;13:227-35.

Ohayon MM, Roth T. Place of chronic insomnia in the course of depressive and anxiety disorders. J Psychiatr Res 2003;37:9-15.

Sanchez C, Papp M. The selective sigma2 ligand Lu 28-179 has an antidepressant-like profile in the rat chronic mild stress model of depression. Behav Pharmacol 2000;11:117-24.

Sarrias MJ, Artigas F, Martínez E, Gelpi E, Álvarez E, Udina C, et al. Decreased plasma serotonin in melancholic patients: a study with clomipramine. Biol Psychiatry 1987;22:1429-38.

Sarrias MJ, Martínez E, Celada P, Udina C, Álvarez E, Artigas F. Plasma free 5HT and platelet 5HT in depression: case-control studies and the effect of antidepressant therapy. Adv Exp Med Biol 1991; 294:653-8.