# THE PSYCHO-NEURO-IMMUNE-ENDOCRINE RESPONSE: A PHYSIOLOGICAL AND PATHOLOGICAL WAY OF LIFE

María Angeles Aller*, Laureano Lorente*, Jorge L. Arias**,
Guillermo Rodríguez-Fabián*, María Soledad Alonso*, Azucena Begega**,
Laudino López**, José Rodríguez-Gómez***, Jaime Arias*

* Universidad Complutense de Madrid, ** Universidad de Oviedo, *** Universidad de Zaragoza

It is proposed that the response of the organism to injury by mechanical energy is made up of three consecutive phases: an immediate or nervous phase, an intermediate or immune phase and a late or endocrine phase. The functions that characterize each one of these three phases could represent the activity of the functional nervous, immune and endocrine systems. This functional concept of the psycho-neuro-immune-endocrine system could make it possible to integrate biochemical knowledge into the organism response to injury.

*La respuesta psico-neuro-inmune-endocrina en fisiología y patología*. Se propone que la respuesta del organismo a la agresión por energía mecánica está constituida por tres fases consecutivas: una fase inmediata o nerviosa, una fase intermedia o inmune y una fase tardía o endocrina. Las funciones que caracterizan cada una de estas tres fases podrían representar la actividad de los sistemas funcionales nervioso, inmune y endocrino. Este concepto funcional del sistema psico-neuro-inmune-endocrino permitiría integrar el conocimiento bioquímico en la respuesta del organismo a la agresión.

Nowadays, the nervous, immune and endocrine systems, which have been considered as separate "systems" can be considered components of a single integrated defence mechanism in which the interactions between systems is as important to understanding adaptation as the interaction within a system (Ader, Cohen and Felten, 1995).

The study of the response of this single integrated defense mechanism of the organism when it is exposed to an old stimulus such as the mechanical energy, could be a method to learn the interactions that exist between these three systems (Lorente et al., 1995).

Acute mechanical trauma can produce different conditions in the human being, acute local inflammation and the polytraumatized patient respectively representing its least and greatest severity. The evolution of both conditions can be explained by the successive alterations which are produced in the blood vascular endothelium and, by extension, in the vascular wall (Lorente et al., 1995). The endothelium, owing to its strategic position, plays an exceedingly important role in regulating the vascular system by integrating diverse mechanical and biochemical signals and by responding to them through the release of vasoactive subs-

Correspondencia: Jaime Arias
Departamento de Cirugía
Hospital Universitario San Carlos
C/ Martín Lagos, s/n.
28040 Madrid (Spain)

tances, cytokines and growth factors (Inagami, Naruse and Hoover, 1995).

Different phenomena are successively produced in the local inflammation, which is considered as a response to post-traumatic necrosis: vasoconstriction and vasodilation (Davies and Hagen, 1993), exudation secondary to an increase of endothelial permeability which is the cause of swelling (Lum and Malik, 1994), diapedesis or cell migration, specially neutrophils, which is associated with phagocytosis and necrosis (Adams and Shaw, 1994) and proliferation with endothelium and vascular wall modelling (Davies and Hagen, 1993), which is associated with tissular regeneration or synthesis of granulation tissue.

The succession of vascular changes could represent three phases of the endothelial response to injury: a first phase, immediate or nervous, characterized by alterations of the vascular tone, that is vasoconstriction and vasodilation, a second phase, intermediate or immune, mediated by the endothelium and represented by the tissular infiltration of molecules and blood cells, and a third phase, late or endocrine, represented by the cellular proliferation which, in the case of healing, involves tissular regeneration or wound repair (Lorente et al., 1995).

This abstraction also makes it possible to consider the evolution of the polytraumatized patient as a succession of three partial responses (Lorente et al., 1995), that is, immediate or vasomotor, which can produce shock (Jacobs and Panic, 1994), intermediate or immune, whose hyperexpression represents the systemic inflammatory response syndrome (SIRS) (Bone, 1995) and late or endocrine, in which the predominance of anabolism, convalescence phase (Shaw and Koea, 1993), or catabolism, with cachetsia (Hassett and Border, 1983; Rennie, 1985), plays the greatest role in its evolution (Figure 1).
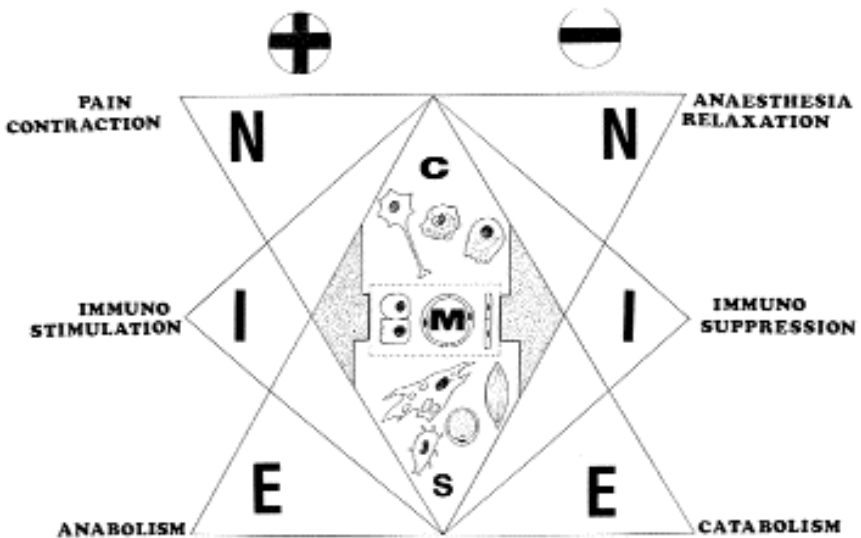


*Figure 1.* The organism, represented by its control (C), mediator (M) and structural (S) components, responds to injury with inflammation, which is considered as a three successive phases functional response: Immediate or nervous (N), intermediate or immune (I) and late or endocrine (E), which, in turn, have a hyperfunctional (+) or hypofunctional (-) expression. C: nervous, lymphoid and endocrine tissue. M: epithelium, endothelium and mesothelium. S: smooth and striatum muscular tissue, connective tissue, osseous tissue and adipose tissue.

This hypothetical similarity of local and systemic responses, although they have different duration, could be attributed to the existence in the organism of a general response mechanism to injury by mechanical energy, which is based on the successive and predominant expression by the vascular wall of functions belonging to the nervous, immune and endocrine systems (Lorente et al., 1995) and which could be common to other pathological processes in which this type of energy is involved, such as heart failure and hypertension.

In arterial hypertension, as a consequence of the chronic action of physical forces, it would be considered that the endothelial cells, the smooth muscular cells and the connective tissue of the vascular wall first express a rapid vasomotor response with enhanced vasoconstriction (neuro), then the cell adhesion, recruitment of mononuclear cells and coagulation predominate (immune) and, finally, a more delayed response would be characterized by hypertrophy and proliferation of muscular smooth cells (endocrine) (Davies and Tripathi, 1993; Davies and Hagen, 1994; Alexander, 1995).

Furthermore, in the evolution of the human heart failure the inadequate preservation of Starling's forces at a microvascular level produces an alteration of the endothelial function that is expressed as an impairment of the contractile and vasodilator response (neuro), changes in permeability and platelet activation (immune) and an increased fibrinolytic activity and basement membrane thickness (endocrine) (Mahy and Tooke, 1995; Lorente, Aller, Arias, in press a).

| Table I | | | | | |
|---|---|---|---|---|---|
| **Inflammatory Response** | | | | | |
| | | **LOCAL TRAUMA** | **POLYTRAUMATIZED PATIENT** | **ARTERIAL HYPERTENSION** | **HEART FAILURE** |
| **Functional Phases** | **I. Immediate or nervous** | – Vasoconstriction (Davies et al, 1993)<br><br>– Vasodilation (Davies et al, 1993) | – Shock (Jacobs et al, 1994)<br><br>– Ischemia-reperfusion (Jacobs et al, 1994) | – Enhanced vasoconstriction (Davies et al, 1994) | – Impaired contractil and vasodilator response (Mahy et al, 1995) |
| | **II. Intermediate or immune** | – Exudation (Lum et al, 1994)<br><br>– Diapedesis (Adams et al, 1994)<br><br>– Coagulation (Davies et al, 1993) | – SIRS (Bone, 1995)<br><br>– MOF (Bone, 1995)<br><br>– DIC (Bone, 1995) | – Cell adhesion (Davies et al, 1994)<br><br>– Recruitment of mononuclear cells (Davies et al, 1994; Alexander, 1995)<br><br>– Platelet activation (Davies et al, 1994) | – Alteration in capillary permeability (Mahy et al, 1995)<br><br>– Platelet activation (Mahy et al, 1995) |
| | **III. Late or Endocrine** | – Fibrinolysis (Davies et al, 1993)<br><br>– Proliferation: • regeneration • granulation tissue (Davies et al, 1993) | – Catabolism (Hasset et al, 1983; Rennie, 1985)<br><br>– Anabolism (Shaw et al, 1993) | – Hypertrophy and proliferation of muscular smooth cells (Davies et al, 1994; Alexander, 1995) | – Increased fibrinolytic activity (Mahy et al, 1995)<br><br>– Basement membrane thickness (Mahy et al, 1995)<br><br>– Hyalinosis (Mahy et al, 1995) |

So, the endothelial response to the injury caused by mechanical energy, the initial insult, could be considered as an old response that essentially represents the consecutive and predominant expression of the nervous, immune and endocrine functions, which "in vivo" are integrated in the response of the psycho-neuro-immune-endocrine system of the organism (Lorente et al., 1995; Lorente, Aller and Arias, in press b). The successive expression by the organism of the nervous, immune and endocrine functions in response to the injury by mechanical energy would mean a similarity of the etiopathogenic mechanisms in pathologies which have been considered different up to now because of the histologic as well as biochemical diversity of the structures involved. This hypothetical integration of different pathological processes caused by mechanical energy into a functional response made up by three phases, immediate or nervous, intermediate or immune and late or endocrine, makes it possible to consider that all of them represent different forms of expression of a response which always has the same meaning, that is, inflammation (Table I).

In this sense, bloodletting, a therapeutical procedure to which Galeno gave great importance to and which was frequently used during the middle age, could represent a method to obtain by a mechanical stimulus, hypovolemics, a systemic neuro-immune-endocrine response whose effect should be considered as beneficial in diverse illnesses which produce intense pain and high fever, although, in contrast, it can also produce severe complications such as weight loss and even death.

The hypothetical similarity of the local and systemic responses when injury by mechanical energy occurs could be attributed to the existence in the organism of a general response mechanism to injury which is based on the successive and predominant expression of the nervous, immune and endo-crine functions, in which case it would be considered that the three "classic" organic systems, that is, nervous, immune and endocrine, must necessary be integrated into each of the phases of this functional response. This fact implies that each one of these systems is able to collaborate in the expression of the three above mentioned functional phases of the organic response to injury (Figure 2).

In addition, different combinations of mediators belonging to the nervous (neurotransmitters), immune (cytokines) and endocrine (hormones) classic systems that would predominantly express the functions that are attributed to each phase could act in the three phases of this general response to injury. This would explain the fact that one mediator by itself participates in different
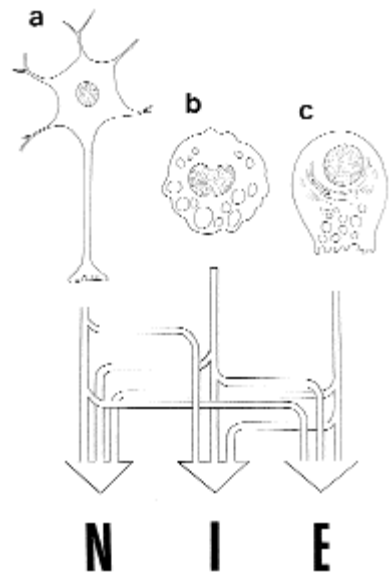


*Figure 2.* Functional concept of the nervous (N), immune (I) and endocrine (E) systems. Function, and not histology or biochemistry, determines the system that is expressed in each phase of the inflammatory response. Representative cells of the nervous (a), immune (b) and endocrine (c) systems are capable of expressing nervous (N), immune (I) and endocrine (E) functions.

phases of this response. In this case, the functions of each phase of this response could be used to propose a functional concept of the nervous, immune and endocrine systems (Lorente, Aller and Arias, in press c) (Figure 2). If the functions which characterize each phase define the corresponding functional systems of the organism, they may similarly make it possible to integrate the biochemical knowledge into the functional meaning which each system has.

Multiples molecules which are considered as fundamental parts of the living organisms have a multifunctional capacity. Nitric oxide (NO) stands out among these molecules and it was named "Molecule of the year" by Science in 1992 (Koshland, 1992). The continuous and more and more complex reviews about NO (Nathan and Xie, 1994; Schmidt and Walter, 1994; Kam and Govender, 1994; Rodeber et al., 1995) are a great challenge when an attempt is made to integrate its diverse functions into the mechanisms that produce most of the physiological and pathological conditions in the human organism. NO is a pluripotential molecule which can fulfill the requirements to be integrated into the functional neuro-immune-endocrine response because, in a first immediate or nervous phase, it is a mediator of analgesia (Nathan and Xie, 1994; Schmidt and Walter, 1994; Kam and Govender, 1994), contraction or relaxation of the vascular smooth muscle (Schmidt and Walter, 1994; Rodeber et al., 1995), myocardial contractility (Rodeber et al., 1995), bronchodilation, relaxation of gastrointestinal smooth muscle and neurotransmission (Nathan and Xie, 1994; Schmidt and Walter, 1994; Rodeber et al., 1995). In the intermediate or immune response to injury, this molecule would be involved in capillary permeability, platelet adhesion and aggregation and leucocyte adhesion (Schmidt and Walter, 1994; Rodeber et al., 1995). And finally, in the later endocrine phase NO regulates endothelial regeneration and smooth muscle cell proliferation (Schmidt and Walter, 1994; Rodeber et al., 1995).

A functional meaning similar to that belonging to the pluripotential molecules would be attributed to the enzymatic systems of the organism which make up complex cascades with a great diversity of functions. By example, Complement activation (Baldwin et al., 1995) would be closely regulated at every step of the acute inflammatory response according to the predominant function which it expresses in the different phases of the rejection. Thus, in the immediate phase (neuro), the smooth muscle contraction with vasospasm ($C_{2b}$, $C_{4a}$, $C_{3a}$ and $C_{5a}$) would predominate, the intermediate phase (immune) would be characterized by the increase of vascular permeability ($C_{2b}$, $C_{3a}$ and $C_{5a}$), increase of adhesion of macrophages, neutrophils and NK cells ($C_{3b}$ and $iC_{3b}$), extravascular migration of monocytes and neutrophils ($C_{5a}$), with degranulation ($C_{3a}$ and $C_{5a}$) and tissue damage from the membrane attack complex ($C_{5b}$-$C_9$). Finally, in the late phase (endocrine) the endothelial cell release of PDGF and bFGF ($C_{5b}$-$C_9$) with proliferation of fibroblasts and smooth muscle cells would predominate ( Lorente et al., in press).

Therefore, Complement activation could express successive and predominant characteristics functions of the nervous, immune and endocrine systems. In this supposition, the different functions of the multiple components of the Complement could be integrated into the inflammatory response with a sense that would facilitate the comprehension of the implied biochemical mechanisms. If the components of the Complement successively express functions considered as nervous, immune and endocrine in a way which is similar and simultaneous to the expression of these functions by the endothelium and, by extension, by the vascular wall during the inflammatory response,

it may be necessary to enlarge the current concept of the nervous, immune and endocrine systems. This would not be limited to the nervous, lymphoid and endocrine classic systems, but rather all the organism would be involved.

These systems would make up a systemic response integrated by the functions considered characteristic of the nervous, immune and endocrine systems (Lorente et al., 1995; Lorente, Aller and Arias, in press b; Lorente et al. in press). This functional concept of the systems implies that the cells and biochemical components of the organism, for example, those which constitute complex enzymatic systems as the Complement, have the property of modifying their functional expression in the successive phases of response to the injury and, for this reason, perhaps the characteristic functions of each phase of this response could make it possible to integrate the current biochemical knowledge into the evolution of multiple pathological processes and therefore into the clinical evolution of the patients (Lorente et al. in press).

The endothelium is a paradigm in regards to the cellular pluripotential activity (Davies and Hagen, 1993; Lum and Malik, 1994; Adams and Shaw, 1994, Inagami and Naruse, 1995). In turn, the endothelial cell makes up a functional union with the epithelial cell in order to form multiple organs of the body (kidney, lung, pancreas, liver), which are functional barriers capable of expressing neuro-immune-endocrine functions during the inflammatory response. So, in lung inflammation, types I and II alveolar epithelial cells can act together with endothelial cells and constitute a functional unit (Simon and Payne, 1995). When there is a noxious stimulus, this barrier or unit successively expresses an early phase, with vasoconstriction and vasodilation (neuro), an intermediate phase with alveolar swelling and accumulation of fibrin and inflammatory cells within the alveolar space (immune) and a late phase with clearance of intraalveolar fibrin and regeneration of alveolar epithelium and basement membrane or impaired fibrinolytic mechanisms and fibrosis (endocrine) (Simon and Payne, 1995). If lung inflammation is considered as a response made up of three functional phases, it would be possible to integrate mediators, such as Complement components, arachidonic metabolites, cytokines, growth factors and hormones, into the functional meaning of each phase.

The succession in the expression of the nervous, immune and endocrine functional systems by the organism could represent the meaning of an ancestral response whose effectivity has made it possible for the organism to persist on the level of cells, tissues, organs and individuals in both physiological situations, that make up the vital cycles as well as in pathological ones (Lorente et al., 1995; Lorente, Aller and Arias, in press a; Lorente, Aller and Arias, in press b). It is tempting to try to establish a comparison between the functional response to the injury of the psycho-neuro-immune-endocrine system which, in essence, is established on basic functions, such as pain-motility (neuro), intra and extracellular digestion (immune) and anabolism-proliferation (endocrine) and the vital vegetal and animal cycles in which these functions are also predominantly expressed by the living organisms in different periods of time (Lorente et al., 1995; Lorente, Aller and Arias, in press a).

## Acknowledgements

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