

Estratto da: New Trends Funct. Neurol. - N° 4 - October-December 1987

functional neurology

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CIC EDIZIONI INTERNAZIONALI

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SUMMARY

It is now well established that a rich mutual exchange of information occurs between some brain regions and vegetative centres located in the brain stem and medulla. Anatomico-clinical data on suprasegmental control of the vegetative nervous system are dealt with here, by briefly reviewing information relevant to the following territories: the frontal lobe and limbic centres, which are located in the forebrain, the hypothalamus, the respiratory, cardiovascular, and micturition centres of the brain stem.

KEY WORDS

Brain stem, frontal lobe, hypothalamus, limbic system, vegetative system.

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INTRODUCTION

Knowledge on the organization of the autonomic nervous system stems from the original description of the sympathetic trunk and the large visceral plexuses, which have long been regarded as a peripheral network of nerve fibres. Well after the discovery of rami communicantes, Langley (1) was the first to define the autonomic nervous system as a structure including both central and peripheral components. He introduced the term pre- and postganglionic, and regarded the whole autonomic nervous system as consisting of a double organization, including a sympathetic and a parasympathetic subset performing opposite tasks. Almost one

century later, this view can still be regarded as being basically true, although it has been expanded by a wealth of experimental data. While morphological and biochemical studies have disclosed the complexity of chemical anatomy in the periphery, anatomical and clinical observations have revealed the existence of a rich network of relay centres for visceral functions, which are located in the central nervous system.

The evolution of anatomical and functional knowledge has brought about parallel changes in terminology. As defined by Langley (2), the **autonomic system** was a purely visceral motor system consisting of "visceral efferent cells and fibres that pass to tissues other than skeletal muscle". This definition excluded visceral afferent fibres, and the term **autonomic** emphasized the independence of visceral motility from other central and peripheral centres. The discovery of visceral afferents, and the understanding of their constant dynamic role in the regulation of autonomic activities allowed more liberal views to take place. According to Hess (3) the term **vegetative system** implied a continuous functional interplay between somatic and visceral functions, which were regarded as different portions of a single integrated neural mechanism. However, from the anatomicofunctional viewpoint the old term **visceral system** is deemed to be the most appropriate, for it implies the existence of a different organization from the somatic system, which gives the viscera a measure of independence from neural control. Three main features differentiate the vegetative system from the somatic (4): (1) Autonomy of the effector organs, which can function without neural innervation; (2) Existence of peripheral reflex connections, which are not mediated in the central nervous system; (3) Neurohumoral control, as many viscera are regulated by hormones secreted into the blood by endocrine glands under neural control. According to Hess' theoretical framework, such definition may appear reductive, as it does not account for some complex vegetative functions, which can be included in the concept of vegetative system. To this respect, however, it is to be considered that, although such integrative functions certainly occur in the central nervous system, their anatomicofunctional relationships with neural control of viscera still need to be cleared up.

Central integration of visceral activity is a well recognized anatomical and physiological phenomenon, involving different suprasegmental regions, from forebrain to brain stem, which integrate behavioural, somatic, and visceral responses. Schematically, it can be assumed that the main centres exerting control upon preganglionic visceral neurones are located in the frontal lobe, the hypothalamus, and the brain stem.

THE FRONTAL LOBE AND RELATED LIMBIC CENTRES

The frontal lobe, "the most mystifying of the major subdivisions of the cerebral cortex" (5), in addition to performing behavioural and cognitive tasks, constitutes the highest level of integration of visceral function. Common clinical practice accounts for the presence of cardiovascular, digestive, and urinary symptoms in patients with a frontal lobe syndrome (see ref. 6); in addition, experimental data are as follows. Andrew and Nathan (7) described the occurrence of disturbances of micturition and defecation in patients affected by frontal lobe syndrome due to intracranial tumors or aneurysms, to penetrating brain injuries, and to leucotomy. Anatomicoclinical correlations allowed these authors to find a relationship between the control of micturition and defecation and a region located in the superomedial part of the frontal lobe, at the level of the genu of the corpus callosum, including the anterior part of the cingulate gyrus. Unilateral or bilateral lesions of this territory (which includes Brodmann's areas 6 and 24) were liable to cause severe urgency and frequency of micturition and incontinence.

Electrophysiological studies have also confirmed that the frontal and cingulate cortices play a role in the control of visceral functions in different mammals, including man (8-14). Anatomicophysiological experiments in rabbits have shown that electrical stimulation of the anterior midline frontal cortex elicits bradycardia and a decrease in blood pressure (15). In the same animals, stimulation of the frontolateral sensorimotor cortex either does not elicit cardiovascular changes or evokes small and variable changes when stimulated. Interestingly, as shown by this study, the active area from which cardiovascular responses are elicited forms the medial portion of the cortical projection area of the mediodorsal nucleus of the thalamus and thus may be involved in the accompaniments of behavioural activities (i.e., learning and memory processes) associated with this nucleus. Cortical influence is also exerted on other visceral functions. Pupillary dilatation can be obtained by stimulation of area 8 (16); sweat secretion and piloerection have been obtained from irritation of area 6, and, in addition, it has been shown that the posterior orbital cortex has a particularly potent effect on cardiovascular functions, respiration, digestive organs, and temperature regulation (see ref. 17). Responses to visceral stimulation have also been observed in the posterior orbital cortex: both vagal and splanchnic electrical stimulations give rise to bilateral responses (see ref. 18). The central pathways are believed to impinge upon neurones located in the dorsomedial thalamic nucleus projecting to the frontal lobe.

Taken together, the afore-mentioned data indicate that the frontal

lobe cortex exerts a complex control on visceral activity. Furthermore, many of the same data have also pointed to the peculiar visceral competence of the orbitofrontal and medial parts of the prefrontal lobe. When considering current anatomicofunctional knowledge, two main territories can be differentiated in the frontal lobe: the orbitofrontal cortex, which is related to "emotional" functions, and contains the cytoarchitectonically distinct transitional or "dysgranular" cortex (Brodmann's area 13); and the convexity and dorsolateral cortex performing "cognitive" tasks, which contain the typical "prefrontal" granular cortex (see ref. 19). The former is also responsible for the integration of visceral functions. To this respect, the close relationship existing between emotional experiences and visceral responses is part of everyday life and needs not be recalled here. In addition, the granular orbitofrontal cortex integrates a number of subcortical afferent pathways, which are closely related to limbic functions. Tract-tracing studies have shown, in fact, that this cortical territory receives a topographically arranged array of subcortical connections from the mediodorsal thalamic nucleus, particularly from the large-celled medial division, and from the ventral midbrain tegmentum. The neurotransmitters of these pathways are poorly known, as it has only been shown that ascending axons from the midbrain contain dopamine and some neuropeptides (see ref. 20). The peculiarity of this ascending afferent organization is emphasized by the existence of direct mesencephalo-thalamic fibres, originating from dopaminergic perikarya in the ventral tegmental area, and terminating in the dorsomedial nucleus itself. Therefore, dopaminergic neurones of the ventral midbrain tegmentum are capable of communicating with the prefrontal cortex either directly or indirectly, through the dorsomedial nucleus. This thalamic centre is more than a simple relay station: in fact, the medial division of dorsomedial nucleus receives rhinencephalic impulses from the amygdaloid complex (which also has direct amygdalofrontal efferent connections), the piriform cortex, the olfactory cortex, and the septal nuclei. The lateral division of dorsomedial nucleus receives reciprocal connections from the prefrontal granular cortex (21), and also afferents from the cingulate gyrus (22). Walker (23) has proposed that the dorsomedial nucleus may integrate somatic and visceral impulses before conveying them to the prefrontal cortex.

Similarly to ventral midbrain tegmental neurones, the amygdaloid complex (chiefly, the basolateral group) can reach the prefrontal granular cortex either monosynaptically, via the ventral amygdalofugal pathway, or indirectly through the dorsomedial thalamic relay. However, in contrast to the ventral midbrain tegmentum, a role of the amygdala in visceral control is well established. The most common response of amygdaloid stimulation in unanaesthetized animals is an acceleration of

the respiratory rate associated with a reduction in amplitude (24). Inhibition of respiration in animals and man has been elicited particularly from ventral parts of the amygdala (12,25). Cardiovascular responses involve both increases and decreases in arterial blood pressure and alterations of heart rate (26). Gastrointestinal motility and secretion may be inhibited or activated, and both defecation and micturition may be induced. Piloerection, salivation, pupillary changes and alterations of body temperature can occur. These responses are both sympathetic and parasympathetic in nature. It is of interest that low level stimulations placed in the amygdala central nucleus are effective in producing potent cardiovascular responses (27), which cannot be induced by similar stimulations of other subdivisions of the amygdala. The central nucleus, in fact, has a peculiar anatomical afferent organization, for it is the recipient of all the dopaminergic input to the amygdala arising from the ventral midbrain tegmentum (see ref. 28).

In summary, physiological and behavioural studies support the view that the orbitofrontal and medial parts of the frontal lobe integrate visceral, limbic and some other complex information. However, a detailed knowledge of the organization of such integrative role is still lacking. A large amount of information processed in the prefrontal lobe originates from subcortical integrative relay centres (such as the dorsomedial nucleus, the amygdala, and the midbrain tegmentum), where it has undergone preliminary modulation. Visceral control is exerted by the prefrontal cortex through direct efferent projections to the hypothalamus, the amygdala, the thalamus, the brain stem, and the spinal cord (29). The corticospinal fibres are believed to lie ventromedial to the corticospinal pathway.

THE HYPOTHALAMUS

The role of hypothalamus in controlling visceral functions is a crucial one. This region is classically regarded to as consisting of a constellation of centres, each of which is devoted to the integration of a specific vegetative or endocrine function. Although this view can be challenged by evidence that the hypothalamus works as a single integrator (e.g., see ref. 30), it reflects the existence of a good deal of detailed knowledge on hypothalamic functions. A critical anatomicofunctional review of this subject is offered by Brodal (31). Schematically, the hypothalamus integrates visceral activities by means of neuroendocrine control and by direct anatomical connections with visceral centres.

Neuroendocrine control is a wide topic, that cannot be dealt with

here (see ref. 32 for a review): afferent information is conveyed by circulating hormones, efferent information is exerted on the pituitary and the remainder of endocrine glands by means of neuroendocrine portal secretion and direct projection to the pituitary.

In addition, the hypothalamus has direct **anatomical connections** with other regions of the central nervous system (see ref. 31). Afferent pathways originate from the hippocampal formation, the piriform and orbitofrontal cortex, the dorsomedial thalamic nucleus, the amygdala, the brain stem (including the reticular formation, the locus coeruleus, the raphe nuclei, the periaqueductal gray, and the nucleus of the solitary tract). Efferent pathways are directed to the anterior thalamic nuclei, the amygdala, the septum, the hippocampus. It is of particular interest that the paraventricular hypothalamic nucleus (and possibly also other hypothalamic subdivisions) sends direct descending projections which branch to a number of vegetative centres, including the periaqueductal gray, the reticular formation, the Edinger-Westphal nucleus, the solitary tract, and the dorsal motor nucleus of the vagus; they terminate in the spinal cord in close contact with sympathetic and parasympathetic preganglionic perikarya (33).

BRAIN STEM CENTRES

In addition to parasympathetic preganglionic neurones which belong to cranial nerves, some different integrative centres for vegetative function have been described in the brain stem. They are thought to be specific subdivisions of the brain stem reticular formation. Most of the early studies on this subject have been undertaken in order to identify the integrative centres of opposite autonomic responses. Such conceptual approach stems directly from the view of the autonomic nervous system as a balanced dual organization of opposite functions (e.g., bradycardia, a parasympathetic effect, is opposed to tachycardia, a sympathetic response). This has led to the identification of antagonistic integrative centres (e.g., cardiac depressor and pressor areas), which are now regarded as a far too schematic simplification. In general, it can be assumed that brain stem autonomic integration is exerted by means of direct efferent pathways to a wide number of rostral and caudal regions; input of information derives from afferent pathways, and also from the transduction of chemical data at the level of the area postrema and of other chemoreceptor regions located outside the blood-brain barrier.

Physiological experiments have revealed the existence of an **inspiratory** area located in the medulla (34), and of an **expiratory**

region just rostral and lateral to it. They are usually referred to as the **medullary respiratory centre** (35). Subsequent stimulation and lesion experiments have led to hypothesize a more complex arrangement (see ref. 36), consisting of an **apneustic** and a **pneumotaxic** centre located in the pons, and exerting hierarchic control on the more elementary caudal centres. On the grounds of more recent anatomical and physiological knowledge, this classic view can still be regarded as being basically correct, although somewhat simple. An updated schematic theory has been proposed by Hukuhara (37), whom the reader is referred to for further data.

Brain stem centres for the control of **cardiovascular function** have also been described. Wang and Ranson (38) and Alexander (39) described a depressor and a pressor region, located, respectively, in the medio-caudal part of the medulla, and in the rostro-lateral medulla and caudal pons. Later studies have challenged this view, and focused mainly on the nucleus of the solitary tract and its vicinity, on the nucleus ambiguus (which is known to contain almost all the visceromotor fibres to the heart), and on the dorsal motor nucleus of the vagus (40). In addition to this, cardiovascular responses can be elicited by stimulation of a number of brain stem regions (including the paramedian reticular nucleus, the raphe nuclei, the nucleus reticularis gigantocellularis, the perihypoglossal nuclei, the lateral reticular nucleus; see ref. 41); however, it is to date quite uncertain whether they represent direct vegetative effects. It must be assumed, however, that cardiovascular integration in the brain stem is not simply arranged in series, as it seems to be the case for respiratory centres, and that a good deal of knowledge on its organization is still lacking (42).

It is presently believed that also **micturition control** is exerted in the brain stem. Barrington (43) discovered a **micturition reflex centre** located in the dorsolateral pontine tegmentum. Bilateral lesions of the dorsolateral pons, just ventral to the internal edge of the superior cerebellar penduncles, resulted in a permanent inability to empty the urinary bladder in the cat (44). Anatomicophysiological studies have also shown that this facilitatory centre for micturition is located in between the locus coeruleus and the nucleus tegmentalis dorsalis (Gudden), in a region corresponding to the nucleus tegmentalis laterodorsalis (Castaldi) (45).

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