Journal of Clinical Neuroscience 18 (2011) 1028–1037

Contents lists available at ScienceDirect

Journal of Clinical Neuroscience

journal homepage: www.elsevier.com/locate/jocn

History

An historical view of the pineal gland and mental disorders

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ARTICLE INFO

Article history:
Received 25 August 2010
Accepted 6 November 2010

Keywords:
History of medicine
Melatonin
Pineal gland
Psychiatric disorders

ABSTRACT

Since Classical Antiquity numerous authors have linked the origin of some mental disorders to physical and functional changes in the pineal gland because of its attributed role in humans as the connection between the material and the spiritual world. The pineal organ was seen as a valve-like structure that regulated the flow of animal spirits through the ventricular system, a hypothesis that took on more vigour during the Middle Ages and the Renaissance. The framework for this theory was "the three cells of the brain", in which the pineal gland was even called the "appendix of thought". The pineal gland could also be associated with the boom, during this period, of certain legends about the "stone of folly". But the most relevant psychopathological role of this organ arrived with Descartes, who proposed that it was the seat of the human soul and controlled communications between the physical body and its surroundings, including emotions. After a period of decline during which it was considered as a mere vestigial remnant of evolution, the link between the pineal gland and psychiatric disorders was definitively highlighted in the 20th century, first with the use of glandular extracts in patients with mental deficiency, and finally with the discovery of melatonin in 1958. The physiological properties of melatonin reawakened interest in the relationship between the pineal gland and mental disorders, fundamentally the affective and sleep disorders, which culminated in the development of new pharmacological agents acting through melatonergic receptors (ramelteon and agomelatine).

1. Introduction

The pineal gland has generated much speculation about its functional role. Its prominent location, its unique characteristics in a context of dual structures and its anatomical appearance have awakened the interest of many researchers, scientists and even philosophers. Since ancient times this "enigmatic organ", as it was called by Van Gehuchten,[1] has been attributed an outstanding role as the connection between the material and spiritual worlds in human beings. In this sense, according to the ancient Indian traditions, humans would be equipped with a "third eye" or mystical organ (the pineal gland), corresponding to the sixth chakra (*ajna*), which would provide a window into the spiritual life of individuals and would enclose the key to its mental power.[2] Thus, the pineal gland would be the key organ for clairvoyance and meditation.[3] This function as a spiritual nexus attained its highest levels of transcendence during the beginnings of modern science in the 17th century. One of the most outstanding proponents of the role of the pineal gland was the French philosopher René Descartes (1596–1650), who put this organ forward as the physical seat of the human soul. The pineal gland not only represented the material seat of the divine spirit, but it was also responsible for the intimate mechanism controlling the precise operation of the human body.[4] Thus, the pineal organ would be actively involved in the dysfunction of this "human machine", particularly in mental disorders.

In this sense, Descartes was an ardent defender of the beliefs of Ancient Greece that passions altered cognitive processes, fundamentally affectivity, and lay behind madness. This belief was maintained during the Mediaeval period and the Renaissance[5] and implicated the pineal organ in this psychophysiological mechanism. Thus, based on these Cartesian postulates, the relationship between mental disorders and the pineal gland as the seat of rational thought has been analysed and studied by numerous authors.

Finally, the major scientific advances that have arisen since the middle of the 20th century, culminating in the discovery of melatonin, the hormone secreted and released by the pineal gland, have, to a certain extent, shown Descartes to be right. For example, within the framework of research into new antidepressant drugs, innovative agents have been found that act specifically on

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doi:10.1016/j.jocn.2010.11.037

melatonergic mechanisms. More than three centuries after Descartes published his postulates, this fluctuating nexus between the pineal gland and mental disorders once more comes to the fore. We analyze this relationship from its origins to the confirmed data that currently support it.

2. The *conarium*, the flow of spirits and the diseases of the soul

Among the many currents of thought and schools of medicine in Classical Antiquity that tried to explain the origin of mental disorders, understood at the time as diseases of the soul, it is worth highlighting the pneumatic current, the methodical school and, of course, the humoural theories of Claudius Galenus of Pergamon (“Galen”; 131–201 A.D.). The hypotheses defended by these schools, however, have roots that delve into the physiological theories about cerebral functionalism defended by some pre-Socratic philosophers, such as Alcmaeon of Croton (540–500 B.C.), who accepted the presence of pores and channels in the brain, or Democritus of Abdera (circa 460–370 B.C.), who defended the existence of vital or mental atoms in perpetual motion within the pores of different organs and tissues.[6] Even Plato of Athens (427–347 B.C.), as set out in his work *Timaeus* (360 B.C.), believed that all human sensations were due to the movement of these atoms through different anatomical vessels. These ideas were consistent with the postulates of the Stoic current of pneumatism, promoted by Diogenes of Apollonia (5th century B.C.), and the theories of Anaximenes (585–524 B.C.) on air as the essential principle of life. This legacy was collected in the Ptolemaic School of Medicine in Alexandria, the most outstanding representatives of which are Herophilus of Chalcedon (circa 325–280 B.C.) and Erasistratus of Ceos (310–250 B.C.). For these authors, air, once inside living beings, was transformed into *pneuma* (or *spiritus*, in Latin). Erasistratus speaks of air (the cosmic *pneuma*), after its transportation from the lungs to the heart, as being transformed in the cardiac muscle into *pneuma zootikon* (*spiritus vitalis*, in Latin), before being subsequently conveyed, through the bloodstream, into the brain, where it would be transformed, in the cerebral ventricles, into *pneuma psychikon* (*spiritus animalis*, in Latin).[7]

Additionally, while the great philosophers of Classical Antiquity (Plato or Aristotle) defended the concept of a rational soul possessing an immaterial character with its illnesses understood as a perversion of the spirit, a kind of moral flaw,[8] the approach to the intimate nature of the human soul by those on medical schools was much more materialistic. Hippocrates of Cos (460–377 B.C.) already considered the soul to be intimately linked with corporality and, therefore, its affections and ills must lack a great many of the supernatural connotations attributed to them. According to Aretaeus of Cappadocia (1st–2nd centuries A.D.) and his pneumatic doctrine, mental illness could be understood as a dyscrasia in the appropriate mixture of the four elementary qualities (hot, cold, dry and wet), which would give rise to an alteration in the dynamics of the *pneuma* or *spiritus*, a product refined from the air breathed in, through the body’s conduits.[8] For their part, the followers of the methodical current, including Soranus of Ephesus (2nd century A.D.) and Caelius Aurelianus (4th–5th centuries A.D.), believed the diseases of the soul lay in a disorder of the correct movement of atoms through their corresponding canals at the cerebral level, either through an increase in their tension (*status strictus*), excessive relaxation (*status laxus*), or an alteration in both (*status mixtus*). For example, the cause of melancholy for Soranus would be narrowing of the body’s canals, thus preventing, at the cerebral level, the correct flow of atoms through them, generating a state of “black choler”.[9]

In this pneumatic and atomistic pathophysiological framework, the pineal gland might have a major role. The first express reference to the pineal gland in Western culture has to be sought in the Anatomy School of Alexandria. In the opinion of Ariëns-Kappers,[3] Herophilus of Chalcedon could well have been the true discoverer of the pineal gland. Herophilus put forward the idea that this organ exercised valvular control, similar to a sphincter, that regulated the flow of the *pneuma psychikon* from the medial ventricle to the posterior ventricle,[10] the location of the *mneme* (memory), according to Aristotle (384–322 B.C.).[11] Nonetheless, there is no direct evidence of these statements as all the writings of the anatomists from Alexandria have been lost and the references to them are in the texts of Galen, where it is said that the “ancient anatomists” were aware of the pineal organ. In either case, this role as a valve, subsequently defended by other authors such as Hippolytus of Rome (circa 170–235 A.D.), later Saint Hippolytus (*Refutation of all Heresies*),[12] would be of the greatest importance in the dynamics of the *spiritus* and, thus, in the genesis of the diseases of the soul.

However, with the emergence of the greatest figure in Classical medicine, Galen, the physiological transcendence of the pineal organ and its relationship with the pathogenesis of mental illnesses would lose ground almost completely. Galen collected together the philosophical–physiological heritage of Greece, changed the pneumatic theory and re-designed a doctrine of humours that would last until the 18th century.[13] Following Plato, the “Master from Pergamon” (Galen) assumes the existence of a rational soul, located in the brain, and speaks of a human faculty (*dynamis*) that corresponds to mental spirits or *pneumata*, extremely subtle material substances. Thus, pneumatized blood in the heart would be led through the *rete mirabile* of the brain and would give rise, in the lateral ventricles (which Galen considers a single paired ventricle, which he named “anterior ventricle”), to the mental pneuma or *spiritus animalis*.[14] For Galen, the brain would act as a kind of hydraulic pump distributing the mental pneuma through the body,[15] but he eliminates the role of the pineal organ as a sphincter and attributes this role to the *vermis superior* of the cerebellum, an anatomic structure that would act as a kind of valve capable of shutting off Silvio’s aqueduct and prevent the passage of the mental pneuma to the fourth or posterior ventricle, the location or seat of memory.[16] According to Galen, the author who provided the first detailed description of the pineal organ (cited in Ref. 17), which he called *konareion* (“pine cone”, in Greek; *conarium*, in Latin), its extracerebral location and its inherent inability to produce movement would prevent it from performing the activities of a valve. In his *De anatomicis administrationibus*, Galen described the anatomy of the *conarium* in great detail, and in Part Eight of his work *De usu partium*, he relegated its functional role to a mere pseudoglandular lymph organ holding together the mass of veins in the brain covering the posterior and dorsal faces of the diencephalon.

In the same way, the aetiology of the diseases of the soul was explained by Galen without reference to the route of animal spirits. Following the postulates of the doctrine of the humours based on the four elements, contained in the *Corpus Hippocraticum* (5th–4th centuries B.C.), Galen defends that the different parts of the body, including the soul, were formed by a mixture, in varying proportions, of the four humours (blood, phlegm, yellow bile and black bile or *atrabilis*); good health would lie in their properly balanced mixture and illnesses, including those of the soul, would be due to a perversion of the blend of humours, with the subsequent predominance or shortfall in certain humours and their respective qualities. Thus, for instance, he states in his work *Quod animi mores corporis temperamenta sequantur* [Why the faculties of the soul derive from the distribution of humours in the body]: “The greater or lesser sagacity in the logical part of the soul depends on the distribution of humours … A warm complexion causes irascibility and this inflames the body’s innate heat; those individuals with a balanced combination of humours have all the movements of the soul tempered and they find it easy to enjoy a peaceful character”.[18]