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Progress in Neurobiology 81 (2007) 237–250

progress in Neurobiology

www.elsevier.com/locate/pneurobio

The neurobiological characteristics of rapid eye movement (REM) sleep are candidate endophenotypes of depression, schizophrenia, mental retardation and dementia

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Received 28 September 2006; received in revised form 14 December 2006; accepted 10 January 2007

Abstract

Animal models are a promising method to approach the basic mechanisms of the neurobiological disturbances encountered in mental disorders. Depression is characterized by a decrease of REM sleep latency and an increase of rapid eye movement density. In schizophrenia, electrophysiological, tomographic, pharmacological and neurochemical activities are all encountered during REM sleep. Mental retardation and dementia are characterized by rather specific REM sleep disturbances. Identification of the genetic support for these abnormalities (endophenotypes) encountered during REM sleep could help to develop specific treatments.

Keywords: Mental illness; Paradoxical sleep; Dreaming

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1. Introduction

Great progress has been made in the treatment of severe mental diseases. The major innovation came from psychopharmacology which by the 1950s, launched the release of chronically hospitalized patients from psychiatric institutions. These chemical forms of treatment were first identified empirically. Although the roots of *Rawolfia serpentina* used as a tranquillizer, had been known since Antiquity, the corresponding chemical agent, reserpine (serpasil), was introduced into the modern pharmacopoeia only in 1954 (Fouks et al., 1954), before being rapidly abandoned because of major hypotensive influences (Freis, 1954). In fact, the current psychopharmacology began slightly earlier, in 1951, when

Abbreviations: 5-HT, serotonin; MHPG, 3-methoxy 4-hydroxy phenyl glycol

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0301-0082/$ – see front matter © 2007 Published by Elsevier Ltd.
doi:10.1016/j.pneurobio.2007.01.004

Henri Laborit (Laborit and Huguenard, 1951) working on artificial hibernation for surgical procedures, identified the tranquillizing impact of 4560 R.P (chlorpromazine) and suggested its use to Jean Delay (Delay et al., 1952) for agitated patients. Chlorpromazine thus became the first specific antipsychotic treatment. The next great progress occurred in 1957 when two clinicians discovered antidepressive compounds. First, N. Kline (Loomer et al., 1957), while dining with tuberculosis surgeons, learned that the patients became euphoric after iproniazide (a later discovered inhibitor of monoamine oxydases). Then, R. Kuhn (Kuhn, 1958–1959) realized that imipramine (later identified as monoamine reuptake inhibitor), a molecule close to chlorpromazine, was also efficient against depression.

In spite of recent progress in the typically symptomatic treatment of psychiatric diseases, the underlying mechanisms of the latter remain to be discovered. Indeed, as with schizophrenia, these diseases are multifactorial with an appreciable polygenic component (Gottesman and Shields, 1967). Hence, researchers are looking for criteria which are characteristic of mental diseases and provide complementary information about their distal genetic roots. One of the most frequent approaches concerns «endophenotypes» (Gottesman and Shields, 1973). These criteria, which can be «neurophysiological, biochemical, endocrinological, neuroanatomical, cognitive or neuropsychological» (Gottesman and Gould, 2003) are «measurable components invisible to the naked eye along the pathway between disease and distal genotype» (Gottesman and Gould, 2003). Endophenotypes represent relatively elementary functional phenomena of any behavior and are also encountered in mental diseases where they can help identify the responsible gene(s) (Hasler et al., 2006).

Endophenotypes should posses some specific criteria. The endophenotype: (a) must be associated with illness in the general population, (b) must be observable despite the fact that the patient may be in partial or complete remission, (c) should be heritable, (d) should segregate with illness within families, (e) should be observed at a higher rate among unaffected family members compared to the general population (Gottesman and Gould, 2003; Berrettini, 2005).

Of course, nowadays, the best means of research involves valid partial animal models of the different psychiatric diseases (Gould and Gottesman, 2006).

We would like to show that a specific sleep stage, namely, the rapid eye movement REM (dreaming) stage, provides a good model for psychiatric endophenotypes. This sleep stage, which also occurs in birds (Klein et al., 1964; Ookawa and Gotoh, 1964; Ookawa and Gotoh, 1965; Tradarti, 1966), is already present in primitive mammals, in partial (Siegel et al., 1996; Siegel et al., 1999; Nicol et al., 2000) or complete (Nicol et al., 2000) form. In all other mammals, it is mainly characterized by cortical rapid low voltage activity, often indissociable from the waking electroencephalogram (EEG) (Aserinsky and Kleitman, 1953; Dement and Kleitman, 1957; Dement, 1958; Jouvet et al., 1959), rapid eye movements generally occurring in bursts (Aserinsky and Kleitman, 1953) and inhibition of muscular activity (Jouvet and Michel, 1959; Berger, 1961). In addition, though mainly studied in animals but also described in humans (McCarley et al., 1983; Miyauchi et al., 1987), phasic waves called ponto-geniculo-occipital (P.G.O.) spikes (Jouvet and Michel, 1959; Mikiten et al., 1961; Hobson, 1964; Michel et al., 1964) and eye movement potentials (E.M.P.) (Michel et al., 1964; Gottesmann, 1966, 1967a,b, 1969) occurs in association with the eye movements (see Callaway et al., 1987; Gottesmann, 1997).

Dreaming is the nearly specific unique mental activity of REM sleep. Indeed, while some dreams have been described during slow wave sleep in addition to the main thought-like mental activity (Foulkes, 1962; Bosinelli, 1995), dreaming is now considered to occur necessarily during underlying REM sleep neurobiological processes even if some electrophysiological criteria are covert (Takeuchi et al., 1999; Nielsen, 2000; Takeuchi et al., 2001). This mental activity is supported by both activating and inhibitory, antagonist yet complementary forebrain processes, mainly supported by the brainstem, the inhibitory processes being significantly decreased during REM sleep as compared to waking (see Gottesmann, 1999, 2005a).

We will consider the relationship which can be established between REM sleep neurobiological criteria and psychiatric diseases. We will successively analyse REM sleep disturbances in depression, schizophrenia and mental retardation-dementia, the last disorders being long considered to constitute the only true neurological syndromes.

2. Results

2.1. Depression

It is likely that Gresham et al. (1965) undertook the first sleep study of depressive patients and found more REM sleep in the first third of the night. Shortly afterwards, Green and Stajduhar (1966) and Hartmann et al. (1966) found a decrease of REM sleep latency at sleep onset, and an increased percentage of REM sleep. Very interestingly, Green and Stajduhar observed a decrease of REM sleep after electroshock treatment (which confirmed results obtained the same year in animals (Cohen and Dement, 1966; Cohen et al., 1967)), and the subjects were cured by this application. Today, the reduced latency of REM sleep appearance which expresses a pressure of this sleep stage, is well established. More recent findings have shown that there is also an increase of eye movement density, thus of the number of rapid eye movements per period of REM sleep, particularly during the first part of night, while the increased eye movements usually appear in the last part of the night during longer-lasting REM sleep periods (Rush et al., 1986). In addition, there are, during sleep, homolaterally theta–delta and bilaterally beta–delta EEG coherence abnormalities in subjects at high depressive risk (Fulton et al., 2000). All REM sleep abnormalities favor development of later depressive episodes (Giles et al., 1988b), and even unaffected relatives show reduced REM sleep latency and increased eye movement density (Giles et al., 1988a; Giles et al., 1993; Giles et al., 1998; Modell et al., 2005). The heritability of these REM sleep characteristics concords well with the endophenotype criteria