The Level of Hypocretin 1 (Orexin A) in Cerebrospinal Fluid and the Diagnosis of Narcolepsy and Other Somnolent Disorders

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Narcolepsy is a chronic sleep disorder characterized by excessive daytime sleepiness, cataplexy, sleep paralysis, and hypnagogic hallucinations (1). A nocturnal polysomnogram, followed by the multiple sleep latency test is suggested for the diagnosis. These tests, performed at a sleep disorders clinic, confirm the daytime sleepiness by showing a short sleep latency of usually less than 5 minutes, as well as an abnormally short latency prior to the first rapid eye movement (REM) period (2). HLA typing also helps the diagnosis. However, the tests often have false-negative and false-positive cases and HLA typing is only supportive (3).

Hypocretin 1 and 2 (orexin A and B) are newly discovered neuropeptides, which were found by two isolated research groups in 1998 (4, 5). Hypocretin-containing neurons exist exclusively in the lateral hypothalamus and project widely to various monoaminergic cell groups in the brain (6). They are considered to be key neuropeptides controlling sleep and arousal states. One of the epochs of the clinical use of measuring the level of hypocretin 1 in cerebrospinal fluid was the finding of an extremely low level in narcolepsy patients and the usefulness of the diagnosis (7, 8). The following reports confirmed the reliability of the measurement of hypocretin level in cerebrospinal fluid in narcolepsy (9–11). The specificity of the test for the diagnosis is 84.2% to narcolepsy-cataplexy subjects and 94.4% to HLA-positive ones (8). Only a small number of patients also have an extremely low level of hypocretin 1, for example in Guillain-Barré syndrome (9) and Hashimoto thyroiditis (10). The accuracy of the test reliability contributes also to the diagnosis of narcolepsy in its early stage and in monosymptomatic or HLA-negative patients (10). Moreover, primary and secondary hypersomnia patients also have a low level of cerebrospinal hypocretin 1 (10, 11). So, the extremely low level of hypocretin 1 strongly indicates narcolepsy or hypersomnia patients in respect of sleep and awakening disorders induced by a hypothalamic lesion. Another interest lies in the possibility of the test to differentiate the hypersomnia state induced by a hypothalamic lesion and consciousness disturbance from other neurological diseases. For this purpose, it is important to measure the cerebrospinal hypocretin 1 level in various somnolent patients. One case of diencephalic stroke was reported to have a low hypocretin concentration (12). The other report was a patient of multiple sclerosis who had bilateral lesions in hypothalamus and the level of hypocretin 1 returned to a normal level when the unilateral lesion was recovered by high-dose methylprednisolone therapy (13).

Hypocretin 1 has also played an important role in energy homeostasis (9) and cardiovascular controlling system (14). The symptoms induced by hypothalamic lesion has been difficult to perceive due to the shortage of confirming methods if the symptoms are really derived from the lesion. Hypocretin 1 is a good marker which indicates the dysregulation or destruction of hypothalamic sleep and awakening system. If it is questionable whether the symptoms come from the hypothalamic lesion or not, the measurement of cerebrospinal hypocretin 1 can provide some information. It also suggests the determination if the symptom is hypersomnia or consciousness disturbance due to the cerebrovascular damage of bilateral hypothalamus in the case of infarction at the top of basilar artery. Further studies using these peculiar neuropeptides are expected in various clinical fields.

See also p 743.

References


