Reduced numbers of corticotropin-releasing hormone neurons in narcolepsy type 1

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Background: Narcolepsy type 1 (with cataplexy) is a rare invalidating chronic sleep disorder caused by a loss of hypocretin neuropeptides, presumed to be due to an auto-immune process. A systematic search for possible involvement of other hypothalamic neurons implicated in sleep-wake regulation has never been performed.
Methods: We systematically quantified immunohistochemically stained sleep-wake related neuronal populations and the presence of microglia in the hypothalamus of narcolepsy type 1 (n=4), idiopathic hypersomnia (n=1) and matched controls.
Results: Biological clock**:** there was no difference in the numbers of vasopressin-expressing neurons in the suprachiasmatic nucleus. Sleep promoting neurons: the density of galanin positive neurons in the ventrolateral preoptic nucleus was stable. Arousal related neurons: we confirmed the hallmark loss of hypocretin-1 expressing neurons and the increased numbers of histaminergic neurons. The density of choline acetyltransferase-expressing neurons in the nucleus basalis of Meynert was unchanged. We found a selective and strong reduction in the number of corticotropin-releasing hormone (CRH)-positive neurons in the paraventricular nucleus (PVN) of narcolepsy type 1 and significant less CRH-positive fibers in the median eminence. While, no alteration was observed in other PVN neurons, i.e. vasopressin, oxytocin, or tyrosine hydroxylase--expressing neurons. Microglial reactions: The presence of ionized calcium binding adaptor molecule 1 tended to be increased in the hypocretin area, but not in any other adjacent area. The human leukocyte antigen-staining was similar in all these areas.
Conclusions: This surprising decrease in CRH neurons may contribute to sleep-wake symptoms and may provide novel targets for diagnostics and interventions.