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The Unfinished Journey with Modafinil and Discovery of a Novel Population of Modafinil-Immunoreactive Neurons

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Abstract

Modafinil, a wake-promoting compound now used worldwide in sleep medicine, was initially regarded as a sedative compound because mice were so quiet with respect to locomotion after receiving it that this behavioral state was qualified as sedation. In the early 1980's when modafinil was first assessed by polysomnography in a cat in our laboratory, surprisingly, the cat spent the whole night awake without even one minute of sleep! This initial observation resulted subsequently in a series of basic and clinical studies in order to define the pharmacological profile of modafinil and its mode of action and, notably, to identify the brain targets by which modafinil acts to promote wakefulness. These studies were undertaken using pharmacology coupled with the *Cerveau isolé* (brain transection) preparation, *c-fos* labelling and knockout mouse models. It was also in this context that we have developed a purified polyclonal antibody against modafinil. We expected that using immunohistochemistry with this antibody would allow us to localize the brain distribution of modafinil dosing. Surprisingly, we found discrete modafinil immunoreactive neuronal populations in several brain areas of modafinil-naive cats, rodents and humans. The most numerous and intensely labeled modafinil-immunoreactive neurons characterized by granular staining were found in the basal forebrain. They shared the regional location with cholinergic and aspartate-containing neurons but did not colocalize with them. In summary, we here present a newly identified neuronal population located in the basal forebrain that has never previously been published and suggests that these modafinil-immunoreative neurons might be involved in forebrain functions such as sleep-wake control and cognition. This paper briefly reviews our journey with modafinil research and presents new unpublished experimental data.