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Why trypanosomes cause sleep disturbances

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African trypanosomiasis or sleeping sickness is a complex disease that involves a constellation of symptoms, but is hallmarked, during disease progression, by the onset of disturbances of sleep/wake alternation during 24 h and by alterations in the organization of sleep. In particular, the patients develop frequent and sudden sleep episodes during the day, and wakefulness episodes during night. A striking feature of the illness is represented SOREM (sleep onset rapid eye movement) episodes, in which the patients go directly from wakefulness to REM sleep without passing through non-REM sleep. Similar alterations have been found in *Trypanosoma brucei brucei*-infected rats, and we are now documenting a relatively early onset of SOREM episodes during the experimental infection. In trypanosome-infected rats, the number of SOREM episodes increases over time and reaches a peak which is coincident with intrusion of sleep into wakefulness and vice versa. We are currently investigating whether the latter changes can help in disease staging by revealing parasite passage across the blood-brain barrier (BBB) and invasion of the brain parenchyma.

Why does trypanosome infection disturb the sleep/wake cycle and sleep organization? Our understanding of the molecules and neural networks that regulate sleep and its alternation with wakefulness has progressed in the last years, highlighting a distributed system with complex interactions. The alternation between sleep and wakefulness is an endogenous biological rhythm, regulated by the master pacemaker located bilaterally in the suprachiasmatic nucleus of the anterior hypothalamus, entrained to environmental light by direct inputs from the retina. Information on circadian timing is transmitted to components of sleep-regulatory circuits.

Current knowledge implicates that neural-immune interaction in specific brain regions are involved in the pathogenesis of the striking sleep disturbances that characterize African trypanosomiasis. As observed in rodent models of trypanosome infection, the parasites do not cross the BBB early in the infection, although they are present in high numbers in the blood. However, trypanosomes accumulate in the choroid plexus and circumventricular organs, which lack a BBB, and cross later the BBB through a multistep process partly regulated by cytokines.

By their localization to circumventricular organs, the parasites, and the inflammatory reaction they elicit, reside for a relatively long period of time very close to the biological clock and to neural centers that regulate sleep. Host-parasite interactions, mediated by diffusible molecules and/or neuronal signaling, could therefore selectively target these structures during sleeping sickness.