NEUROPHARMACOLOGY OF THE SLEEP–WAKING CYCLE

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1. INTRODUCTION

There are two main problems related to the neuropharmacology of sleep: Is it possible to induce physiological sleep, at will, and for a predetermined duration, with a drug in a normal intact animal? The answer to this question is still negative. Neither in animals nor in man do we have yet the right hypnogenic drug or the combination of drugs which will induce at any time and for any duration the delicate and harmonious succession of the different stages and states of sleep. However, neuropharmacology has allowed us to dissect some of the intimate mechanisms underlying the sleep–waking cycle since some drugs may suppress both states of sleep, or suppress paradoxical sleep (ps) selectively, or restore physiological sleep in an insomniac cat.

Our answers to these two problems explain the organization of this chapter. First I will summarize the present main theories of sleep. They seem either contradictory or complementary since we do not yet understand the intimate mechanism of sleep. This ignorance is responsible for the absence of any real hypnogenic drug. Thereafter I will outline the results of the neuropharmacological dissection of sleep mechanisms: the results obtained with drugs whose mechanisms of action are rather “specific” will be described first, while the results obtained with other drugs whose central mechanisms of action are unknown or too complex will be summarized later. This review will be devoted exclusively to animal experiments. The following recent symposia or reviews contain references pertinent to the subject: Fuxe and

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2. THE SLEEP–WAKING CYCLE IN THE CAT

Since the chronic cat is the main experimental animal with which most of the recent advances in the neurophysiology and neuropharmacology of sleep have been obtained, I will summarize below the main qualitative and quantitative characteristics of the sleep–waking cycle which have been collected with polygraphic methods using continuous cortical and subcortical recordings together with recording of neck muscle activity and of the eye movements using electrooculographic methods. These recordings have provided us with a broad spectrum of regional electrical activity which is characteristic of the delicate intricacy of the different systems entering into play during physiological sleep. It should be emphasized here that the appearance of cortical spindles or slow waves is not sufficient alone to characterize “slow-wave sleep.” Thus, it is evident that the old pharmacological techniques using “barbiturate sleeping time” in rats, or “loss of righting reflexes” in mice, or “behavioral sleep” as dependent variables are no longer useful. The main polygraphic features of the sleep–waking cycle in the cat are shown in Fig. 1. In addition to the alterations of cortical activity, from arousal to drowsiness with some slowing of the frequency of the cortical waves, to stage 1 (with spindles) and stage II (high-voltage 2–3 Hz slow waves), some subcortical patterns also permit us to assume that the slowing of cortical activity belongs to physiological sleep. High-voltage sharp waves appear periodically in the pontine reticular formation, the lateral geniculate, and the occipital cortex (pontogeniculate activity) (PGO). This PGO activity appears either during slow-wave sleep (stage II) (isolated PGO, so-called “slow sleep with phasic activity”), or immediately before and during PS. Paradoxical sleep occurs spontaneously every 25 min during sleep and lasts for 6 min. Thus, I shall use the term “physiological sleep” (after any pharmacological alteration) only if we can record the same periodic and harmonious succession of the states of sleep that are observed under control conditions. Hypersomnia would be defined as a state in which both SWS and PS increase significantly above the control level, since the quantity of sleep is remarkably constant in laboratory cats recorded under standard conditions. Since many drugs may increase cortical synchronization only (but may suppress isolated PGO or PS), we shall call this state either “increased slow-wave sleep” (if isolated PGO still occurs) or “increased cortical synchronization” if the pattern of cortical activity is different from normal sleep. If this state is accompanied by an obvious behavioral sedation, it will be called