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The locus coeruleus: actions of psychoactive drugs

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Summary. The locus coeruleus is one of the most thoroughly investigated mammalian brain areas. Its fibers innervate large parts of the neuraxis, in particular, areas involved in cognitive functions such as the cortex and the hippocampus. A role of locus coeruleus has been proposed in such processes as memory, the control of vigilance, blood pressure and others. Results obtained in this and other laboratories demonstrate that the firing rate of locus coeruleus neurons is affected by a great number of psychoactive agents such as antidepressants, minor tranquillizers, neuroleptics, psychostimulants and certain psychogeriatric drugs. We have attempted to correlate the data obtained on the cell bodies of locus coeruleus with studies reporting effects on terminal areas and thereby gain an overall view of the action of the above mentioned drugs on this cell system. The activity of noradrenergic neurons in locus coeruleus is thought to correlate with the level of cortical vigilance. Special emphasis is placed on the finding that a number of drugs which exert a positive effect on cognitive functions in man and animals increase the firing rate of the rat locus coeruleus neurons.

Introduction

Since the discovery of noradrenaline in the locus coeruleus (LC) this group of neurons has received ever increasing attention by neurobiologists. Today the noradrenaline-containing LC-system is undoubtedly one of the best documented neuronal systems in the brain. The number of functions which have been proposed and the knowledge of the biological properties of this system which has been acquired in the past 5-10 years have grown enormously.

The proposed functions of LC encompass such diverse processes as memory and learning[2], attention[38,40,41], the sleep-wakefulness cycle[33], extinction[39] and others. In the past 2 years research has focussed again on the theory which states that this cell group is involved in the regulation of vigilance and attention[25,32,33,36,41]. Support for this notion has come from several lines of research. In single cell recording studies performed in freely-moving rats and monkeys it has been shown that the activity of LC-neurons correlates with the level of vigilance[4,12,22,30]. Highest levels of cellular activity were seen during wakefulness and lower firing rates were observed when the animals were drowsy or in slow-wave sleep. LC-neurons were activated by a variety of sensory stimuli[5] and changes in electrocortical activity were anticipated by changes in LC-neuronal firing activity[4,5]. The relationship between LC-neuronal activity and vigilance points to a link between arousal and the release of noradrenaline. Behavioral and electrophysiological evidence supports the argument that LC plays a role in attention[41]. In electrophysiological studies it has recently been shown that noradrenaline may facilitate the transfer of afferent information within the cerebral and cerebellar cortical circuitry by enhancement of the 'signal-to-noise' ratio[57,58]. Thus the LC-system may serve as a kind of 'filter' which separates behaviorally relevant from irrelevant, distracting signals and in this way augments and focusses attention. Further evidence for a role of the central noradrenergic systems in the control of arousal comes indirectly from pharmacological studies. The 'classical' catecholamine hypothesis of depression is based on the assumption that noradrenergic neurotransmission is linked with mood and behavioral alertness. The known noradrenaline potentiating property of classical antidepressants and of amphetamine is in keeping with this notion. Interestingly, classical antidepressants[42,48] and amphetamine[27] depress the spontaneous firing of noradrener-

gic LC-neurons in the acute experiments in the anesthetized rat. It has been suggested that this effect results from feedback inhibition of these neurons which is probably mediated by presynaptic alpha-receptors[54].

For the electrophysiologist, the locus coeruleus is an attractive substrate to study the action of psychotropic agents. Its neurons can be readily identified and the activity of single neurons can be recorded during prolonged periods. The cell group appears to function in concert as an homogeneous ensemble, showing uniform reactions to the administration of psychotropic agents, classical neurotransmitters and several peptides. In the past 3 years we have been studying the action of a number of psychoactive drugs on the activity of these neurons. By tradition, indeed almost by necessity, experimental investigations study one part of a generally isolated system. Whilst the present study does not make exception to this rule we have attempted to correlate the data obtained on the cell body of the noradrenaline pathways with studies reporting effects in terminal areas and thereby gain an overall view of the action of the drugs tested on the noradrenergic system.

Methods

The experiments were performed on male rats (RAI f (SPF), 280–320 g) anesthetized with chloral hydrate (400 mg/kg i.p.) and mounted in a stereotaxic apparatus. Additional anesthetic was supplied when necessary. Body temperature was maintained between 36.5 and 37.5 °C. A 3-mm burr hole was drilled in the skull over the approximate coordinates of the LC. Extracellular single cell recording was accomplished by means of single barrel glass electrodes (tip size: 1–3 μm) filled either with 4 M NaCl or with a solution of 2 M NaCl saturated with Fast Green. The LC was approached stereotactically using the following coordinates: 1.7 mm posterior to the interaural line; 1.1 mm lateral from the midline and 6.8–7.4 mm ventral from the dura. Action potentials recorded from single cells were amplified and displayed on an oscilloscope. The spikes were separated from the noise by means of a window discriminator. The number of spikes was integrated over periods of 60 sec. The output of the integrator was displayed on a penrecorder. The average firing rate of individual neurons was thus recorded in histogram form as the number of spikes per 60 sec. Noradrenergic neurons in LC were identified according to 5 criteria; a firing frequency of 0.5–6 spikes per sec; a long-lasting positive-negative action potential (2.0 msec) which was longer than that of the non-noradrenergic neurons found near the area of LC; location just below the 4th ventricle, a zone of electrical silence; response to noxious stimulation of the rat's tail or leg with brief burst of firing followed by a prolonged period of firing inhibition; strong reduction or even total suppression of activity 3–10 min following the i.p. administration of either desipramine or amphetamine. In some experiments, the electrode position was marked by the ejection of Fast Green and this confirmed the location of the recorded neuron in the LC during subsequent histology. Only 1 neuron was investigated per rat. When a LC-neuron was found, its activity was recorded during a control period lasting 10–15 min. Following this period, drugs were administered i.p. in cumulative doses at intervals of 25–30 min. All drugs were dissolved in physiological saline solution and administered in a volume of 0.1 ml per 100 g b.wt by the i.p. route. The effect of each dose of a drug was determined separately by comparing the mean firing rate recorded 20–25 min. after injection with the mean firing rate observed during the entire period of control recording. The drug-induced change of firing was expressed as percentage of the cells' pre-drug activity. In some experiments an i.p. injection of either desipramine or amphetamine (3–10 mg/kg b.wt) was administered at the end of the experiment. The spontaneous cell firing was then recorded for another 5–10 min.

Results

The identification of noradrenergic neurons in LC

Neurons with the electrophysiological characteristics outlined above were found to be located exclusively within the area of the locus coeruleus. On each electrode track which passed through LC the slowly firing noradrenergic cells having long lasting action potentials could be easily identified mostly on the basis of their firing characteristics alone: these characteristics clearly distinguished these cells from other types of cells which were firing at a higher rate and displaying action potentials of shorter duration. In addition the response of the neurons in the LC area to painful stimulation of the tail or leg clearly differentiated the noradrenergic neurons from other cells. Whereas the noradrenergic slowly firing cells showed a brief phase of excitation followed by a prolonged phase of complete firing inhibition, the fast firing neurons were either excited or did not respond. A few slowly firing cells which had the typical firing characteristics of noradrenergic neurons did not respond to noxious stimuli. They were not included in this study. In those instances in which desipramine was administered at the end of the experiment, the great majority of neurons was either partially or totally inhibited by this drug. At the dose of 3 mg/kg only 1 out of 18 LC-neurons did not respond with a reduction in firing and at a dose of 10 mg/kg, 1 out of 20 neurons failed to reduce its firing rate. Most other neurons completely stopped firing.

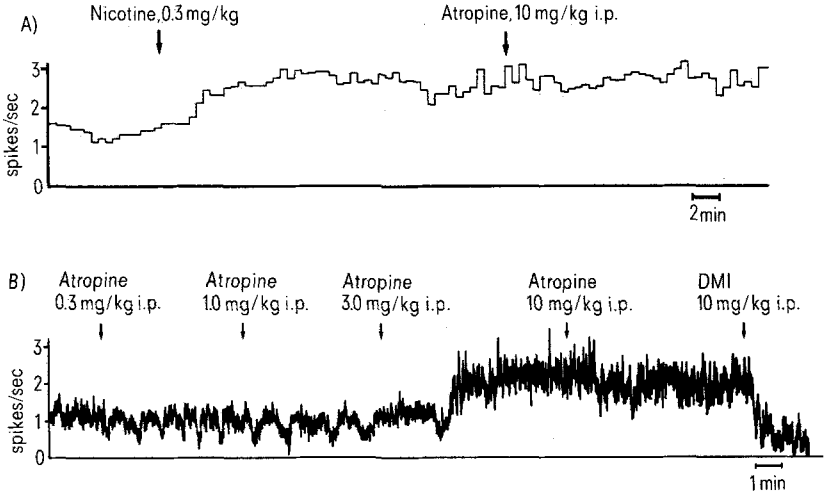

Figure 1. *A* The activating action of nicotine on the firing rate of a noradrenergic neuron of the rat locus coeruleus is depicted. Atropine does not reverse the effect of nicotine. *B* The action of cumulative doses of atropine on the discharge rate of a single LC-neuron is shown. Whereas low doses (0.3 and 1 mg/kg) have no effect, an activating effect is seen with a dose of 3 mg/kg. Desipramine (DMI) strongly depresses this neuron.

Effects of drugs

Nicotine. Administration of nicotine was found to exert a potent excitatory action on LC-neurons (figs 1A and 2B). In the dose-range from 0.01 to 0.3 mg/kg the drug-induced activation became more pronounced with increasing doses of nicotine (n:6–8). With higher doses however, the drug exhibited a decline in effectiveness in causing activation. The excitatory action of nicotine had a short latency between 1.5 and 2 min. The administration of atropine (10 mg/kg, i.p.) 10 min. following the injection of nicotine did not reverse the nicotine-induced increase of LC-neuronal activity (fig. 1A).

Physostigmine. Physostigmine was tested at doses of 0.1 (n=9) and 0.3 mg/kg (n=14). At the lower dose, the compound did not induce any notable change of the neurons' discharge rate. With the higher dose, 8 of the 14 neurons investigated were excited, 4 neurons were depressed and 2 neurons were unaffected. Of the neurons which were excited, the mean increase in firing rate was 70%.

Atropine and scopolamine. Atropine was investigated on 16 LC-neurons. With low doses (0.3 mg/kg, n=7 and 1.0 mg/kg, n=7) no significant change of LC firing was noted (fig. 1B). With 3 mg/kg 3 of the 7 neurons tested increased their firing rate (fig. 1B) and the remaining cells were unaffected. At 10 mg/kg, 5 out of 7 neurons were activated with a latency of onset of 3–8 min. The other neurons showed no alteration of their firing rate. All 3 neurons investigated at a dose of 30 mg/kg increased their firing rate in response to the drug. The mean increase in firing was 25% at a dose of 10 mg/kg and 44% at a dose of 30 mg/kg. Scopolamine (10 mg/kg) produced an increase of firing rate of 5 out of 6 neurons studied. The firing rate increase varied between 26 and 136%. The latency of the activating action of scopolamine varied between 4 and 16 min. In contrast to atropine and scopolamine, methylscopolamine (10 mg/kg) did not alter the discharge rate of any of 6 neurons investigated. In 2 of these experiments, scopolamine (10 mg/kg) increased the firing rate of LC-neurons when administered 15 min. after the injection of methylscopolamine.

Haloperidol and chlorpromazine. Haloperidol (n:3–10) elicited a dose dependent increase of the firing rate of LC-neurons (fig. 2A). The threshold dose was around

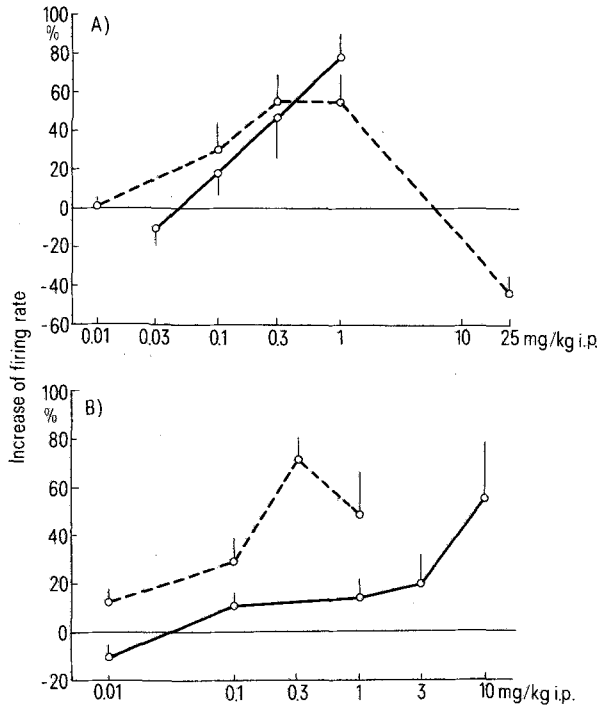

Figure 2. *A* Actions of haloperidol (solid line) and chlorpromazine (dashed line) on the mean discharge rate of noradrenergic neurons of LC. *B* The activating effect of nicotine (dashed line) and caffeine (solid line) on the mean discharge rate of LC-neurons is depicted.

0.1 mg/kg and with 1.0 mg/kg the mean firing rate was increased by 80%. Chlorpromazine also stimulated LC-neuronal activity in the dose range from 0.1 to 1 mg/kg (n:5–8). However this activation was reversed to firing inhibition at the much higher dose of 25 mg/kg (fig. 2A).

Caffeine. Caffeine in doses up to 3 mg/kg i.p. led to a relatively weak activation of LC-neuronal activity (fig. 2B). At 10 mg/kg a marked activation of LC-neuronal activity was seen (n = 9). Interestingly, similar to nicotine, higher doses were less effective in increasing firing rate.

Strychnine. Strychnine at a dose of 1 mg/kg i.p. produced a nonsignificant 5% increase of the mean discharge rate of 8 LC-neurons tested.

Desipramine. In agreement with previous reports[42,48] desipramine was found to inhibit the majority of neurons tested (n: 18–20). This firing depression was found to be dose-related (fig. 3). At a dose of 30 mg/kg all neurons ceased firing. Since neurons could not be held for much longer than about 1 h, recovery from firing depression was never observed.

Psychogeriatrics. We have reported previously that the 3 nootropic agents vincamine, piracetam and hydergine activate LC-neurons[43]. The table summarizes these findings.

Discussion

In their pioneering work, Aghajanian and collaborators have shown that the activity of noradrenergic cell bodies in LC can be recorded and that these neurons exhibit certain electrophysiological and pharmacological properties which allow an unambiguous identification in situ[27,42]. Using their criteria of identification we could confirm in several hundred recordings some of the basic electrophysiological properties of this neuronal group. We have found that the spontaneous firing rate varies between 0.5 and 6 Hz and that the duration of their action potentials is around 2 msec. The mean activity determined in 4-month-old rats was found to be 2.4 Hz (Olpe and Steinmann, unpublished observation). Other laboratories have come to similar conclusions[19,27].

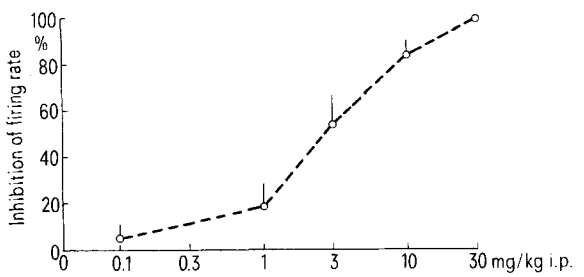

Figure 3. The dose-dependent inhibiting effect of desipramine on the mean firing rate of LC-neurons is shown.

In the anesthetized preparation the spontaneous firing rate of LC-neurons is remarkably constant. After the animal was anesthetized we found that additional administration of anesthetic usually had no significant effect on the activity of a recorded neurone. In some instances we noticed a reduction of firing rate immediately following the i.p. drug administration but recovery from depression occurred within a few min. In a few cases we observed a very pronounced activation of the neurons' discharge rate preceeding an animal's death. Apart from these changes, the spontaneous firing rate was always fairly constant. This contrasts with the discharge characteristics of these neurons in the awake animal where their activity has been shown to correlate with the level of the animal's vigilance and where all kind of sensory stimuli lead to a temporary activation of these neurons[4,5]. It thus seems that anesthesia leads to a stabilization and regularization of the neurons' activity which brings the advantage that even small drug-induced changes can be detected. On the other hand, we do not know yet whether the reactivity of these neurons to systemically applied drugs is basically changed by the anesthesia. To answer this question, we need comparative studies on drugs under the two experimental conditions. With the exception of strychnine, all psychoactive agents tested in the present study were found to affect the discharge rate of LC-neurons. Drugs of a particular class appear to exert a uniform effect on LC-neuronal firing: the classical antidepressants[42,48] and minor tranquillizers[28] have an inhibitory influence whereas certain nootropic agents[43], neuroleptics and some psychostimulants like caffeine and nicotine activate LC-neurons. It should be noted however that the number of drugs investigated in each class of drugs is small and therefore one has to await further investigations before this statement can be generalized. The drugs' action on neuronal discharge is just one aspect of their effect on a given cell system. Each drug potentially has multiple pre- and postsynaptic sites of action which are crucial for the resulting 'effect' on that system. In the following discussion we shall discuss the present findings in terms of the drugs' global effect on noradrenergic transmission of the LC-system.

Classical antidepressants and monoamine oxidase blocking drugs inhibit LC-neuronal firing in a dose-dependent fashion[42,48]. The electrophysiological findings are consistent with biochemical investigations showing that tricyclic antidepressants slow down noradrenaline turnover in the acute experiment. Despite their depressant presynaptic activity on LC-neurons, antidepressants are generally thought to

potentiate noradrenergic transmission at synaptic terminals. Evidence supporting this conclusion derives from a study in which the action of desipramine on the firing rate of postsynaptic neurons was investigated[31]. It was shown that hippocampal pyramidal neurons which are inhibited by LC-stimulation are suppressed following an i.p. injection of desipramine. This effect was blocked either by LC-lesioning or by pretreatment with reserpine and α-methyl-p-tyrosine. The mechanism through which antidepressants inhibit LC-neuronal activity is not known. It has been postulated that this effect is due to an action of noradrenaline on α-receptors located on LC-neurons mediated by axon collaterals[11].

As with the antidepressants, amphetamine has been shown to reduce the firing rate of LC-neurones[27] while potentiating noradrenergic transmission. It has been suggested that amphetamine, by increasing the synaptic concentration of noradrenaline, initiates neuronal feedback inhibition of LC-neurons[27]. Thus amphetamine shares with antidepressants its inhibiting action on LC-neurons and its potentiating effect on noradrenergic transmission.

Clonidine is another potent inhibitor of LC-cell-firing[53]. In contrast to amphetamine its action is associated with behavioral sedation[21]. Similar to the antidepressants, clonidine evokes a reduction of noradrenaline turnover in brain[47]. The systemic administration of opiates has been shown to be followed by a reduced activity of LC-neurons[8,45]. Various biochemical studies, though somewhat contradictory, indicate that opiates can alter noradrenaline-levels and -turnover[13,37,49,52]. Whereas clonidine is thought to act through activation of α_2-receptors located on LC-neurons, the depressant effect of opiates is probably mediated through the opiate receptors located on LC-neurons[45].

Noradrenaline turnover was also found to be decreased by an other important class of psychotropic agents, the benzodiazepines, although relatively high doses were required if the subjects were not stressed[15,16,55]. Two representatives of this class of compounds namely diazepam and chlordiazepoxide have been shown to reduce cell firing in locus coeruleus[27]. The authors speculate that the noradrenergic neurons of the LC play a role in anxiety and that the anxiolytic pharmacological effects may in part be the result of the suppression of LC-unit activity. However, in view of the rather high doses necessary to inhibit noradrenaline turnover and since the role of LC in anxiety has been debated[20], it is questionable whether LC is indeed one of the therapeutically crucial sites of action of benzodiazepines. The site and mechanism of action through which benzodiazepines affect LC-neurons is not known. It is conceivable that they act by potentiation of a tonically active gabaergic input on LC-neurons. In keeping with this hypothesis, LC-neurons have been shown to be sensitive to the depressant action of microiontophoretically administered GABA[29].

A number of compounds exert an activating action on LC-neurons. We have reported previously that 3 psychogeriatric agents, namely vincamine, piracetam and hydergine increase the mean discharge rate of LC-neurons in the anesthetized rat[43]. We speculate that this effect may be linked to some of these drugs' beneficial therapeutic effects on cognitive function or mood. The present results extend the list of compounds which produce an activation of LC-neurons. Some of them are also claimed to affect cognitive function namely nicotine, physostigmine and caffeine. The mechanism through which all these drugs exert their stimulating action on central noradrenergic neurons is not known. In view of their structural dissimilarity it is very likely that different mechanisms are involved. Our findings on physostigmine and nicotine confirm previous reports[17,18] and are in keeping with the postulated excitatory input of cholinergic fibers impinging on LC-neurons. Studies performed with the microiontophoretic technique led to the conclusion that the cholinergic receptors located on LC-neurons are of a muscarinic type[17]. The nicotine-induced LC-activation is thought to be mediated indirectly since these cells were reported to be insensitive to microiontophoretically applied nicotine[17]. We recently confirmed this finding (Olpe, unpublished observation). It has been hypothesized that the activating action of nicotine on LC-neurons may be linked to the drug's arousal-producing properties[18]. The very short latency of the nicotine effect reported here may suggest that the primary site of action is located peripherally. Interestingly, not all LC-neurons reacted with activation to the administration of physostigmine. This is the only compound that we tested so far to which LC-neurons did not respond uniformly. The number of neurons tested is too small to draw any firm conclusions. These results raise the possibility that LC-neurons are not uniformly innervated by cholinergic fibers. Unexpectedly, both atropine and scopolamine in high doses also activated LC-neurons. This effect was not mimicked by methyl-scopolamine which does not penetrate the blood-brain barrier. These findings are in keeping with biochemical studies showing that both physostigmine and high doses of muscarinic antagonists increase the turnover of noradrenaline in brain[14,34]. Our observation that low doses of atropine are inactive in changing the firing rate of LC-neurons confirms a previous investigation and supports the notion that the cholinergic input on LC-neurons is probably not tonically active since one would expect to see an inhibitory effect on LC-neurons if this were indeed the case[17]. Since microiontophoretically administered atropine does not affect LC-neuronal activity[17], the

stimulating property of high doses of atropine is probably mediated indirectly. Its mechanism of action remains to be elucidated.

LC-neurons are not only activated by psychogeriatric agents but also by three representatives out of the class of neuroleptic agents, haloperidol, chlorpromazine and by clozapine[51]. It has been known for quite some time that various neuroleptic agents interact with central noradrenergic systems at both the pre- and post-synaptic level. This evidence derives mainly from biochemical studies[6,9,35]. Systematic electrophysiological investigations on the action of neuroleptics on the main noradrenergic nucleus of the brain, the locus coeruleus, have not been available so far. We found that haloperidol and chlorpromazine in the lower dose-range have a similar potency in activating LC-neurons. These findings contrast with many investigations on the interaction of the two compounds with central dopaminergic systems in which haloperidol is usually much more potent than chlorpromazine. Interestingly chlorpromazine inhibited LC-neurons at the highest dose tested. It appears to be the first drug reported to have a biphasic effect on LC-neuronal discharge. In keeping with these electrophysiological findings are numerous biochemical studies which demonstrated that several neuroleptics increase the turnover of noradrenaline[6,9,35]. On the basis of these observations, it has been speculated that the accelerating action of neuroleptics on central noradrenaline turnover is presumably due to blockade of central noradrenaline receptors[3,9]. This conclusion is corroborated by electrophysiological findings which showed that the inhibitory effects of noradrenaline are antagonized by antipsychotic drugs[23,24]. The net effect of neuroleptics on noradrenergic transmission is unclear. Although the firing rate of noradrenergic neurons is increased, it is unknown to what extent the presynaptic activation is counteracted by postsynaptic blockade of the adrenergic receptors.

The methylxanthine caffeine was found to activate LC-neurons. Evidence accumulated recently suggests that behavioral and other actions of methylxanthines may be mediated through the blockade of adenosine receptors[50]. Adenosine itself inhibits the firing of most neurons in brain[46]. If LC-neurons were to be under a tonic, inhibitory influence of adenosine, then the action of caffeine should be an excitatory one. This remains speculation at present. Irrespective of its site of action, the present electrophysiological findings are consistent with biochemical investigations in which caffeine has been shown to increase the concentration of brain noradrenaline metabolites and hence probably its turnover.

The preceeding discussion clearly demonstrates that the interpretation of single cell recording data has to include information on the drugs action observed in other types of electrophysiological and biochemical experiments. The overall effect of a drug on noradrenergic transmission does not necessarily reflect the effect on firing of LC-neurons. Of all the drugs discussed so far, the following compounds probably facilitate noradrenergic neurotransmission of the LC-system, namely: caffeine, nicotine, physostigmine, amphetamine and the antidepressants (tricyclics and monoamine oxidase blocking drugs). With regard to the above-mentioned nootropics, their effect on noradrenergic transmission remains to be elucidated although one may tentatively assume that they facilitate it.

The finding that several drugs which are said to positively influence cognitive functions all activate LC-neurons and in turn probably facilitate synaptic transmission raises the question whether these phenomena are causally linked. As mentioned above, increased firing rate of LC-neurons has been shown to correlate positively with the animals' vigilance[4]. Increased noradrenergic transmission in turn has been shown to improve information transfer in brain by increasing the 'signal-to noise' ratio. Finally, at the behavioral level, experiments strongly suggest a role for LC in the control of attention. Given these facts it is tempting to speculate that the stimulating property of some of the above-mentioned drugs on LC-neurons may be coupled with some of the drugs' beneficial effects on cognitive functions.

There are indications of an age-related reduction of noradrenergic transmission in animals and man. In human brain noradrenaline content correlates negatively to age[1]. In the aged rhesus monkey cortical catecholamine synthesis is reduced by at least 60% in all sensory and association areas[26]. In the rat we recently demonstrated an age-related attenuation of LC-neuronal firing[44]. Taken together, these findings support the hypothesis that the central noradrenergic system arising from the locus coeruleus may show a functional impairment in the aged mammalian brain. It has been speculated that a functional impairment of LC-neurons may be causally linked with an im-

Percentage change of the mean discharge rate of rat locus coeruleus neurons induced by 3 psychogeriatric agents (cumulative administration; $\bar{x} \pm$ SEM)

	0.1	0.3	1.0	3	10	30	100	300	1000
Vincamine	7.7 ± 12.3	11.7 ± 12.8	80.5 ± 24.3	47.8 ± 24.3	51.6 ± 17.1	51.5 ± 11.2			
Hydergine	8.1 ± 5.3	26.5 ± 17.2	68.8 ± 15.1	59.3 ± 11.9	52.6 ± 10.4				
Piracetam							4.2 ± 5.9	28.2 ± 8.3	39.3 ± 11.5

paired information processing in brain[56]. Psychogeriatric agents may mediate part of their beneficial therapeutic effects by stimulating their activity. Clearly, further electrophysiological and behavioral studies are required to either support or reject this hypothesis.

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EEG and sleep in aged hospitalized patients with senile dementia: 24-h recordings

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Summary. Polygraphic recordings of wake and sleep were performed on 10 partly bed-ridden, severely deteriorated patients with senile dementia. Compared with healthy elderly persons these subjects showed less SWS (slow wave sleep, characterized by high amplitude, slow EEG waves), less REM sleep (rapid eye movement sleep, usually accompanied by dream activity) and poorly organized stage 2 sleep (no sleep spindles, i.e. phasic EEG activity with a frequency of 12-14 Hz). Six of the 10 patients had no dominant alpha rhythm during wakefulness; this seemed to be related to their more deteriorated clinical state, to still less SWS and REM sleep and more time spent in stage 2. The basic NREM-REM cycle of sleep, i.e. the regular alternation between non-REM- and REM-periods, could still be distinguished, however, and showed similar average temporal characteristics as in healthy old and younger people. Similarly, although sleep was severely fragmented in most patients and many sleep episodes occurred during the day, the day-night alternation of wakefulness and sleep was maintained in the sample as a whole.

With advancing age, sleep is subjectively judged to be less deep and less refreshing, and interruptions are more frequent. Objectively there is less slow wave sleep (SWS), particularly stage 4, and less rapid eye movement (REM) sleep. The polygraphic trace shows a decreased overall amplitude and slower and less pronounced spindles, with long periods of theta activity[12,22]. A high percentage of sleep-related respiratory disturbances may contribute to the more interrupted nature of sleep[2]. Furthermore the alpha waves during wakefulness are found to be decreased in amplitude, slower in frequency and fewer in number. There is a progressive increase in slow wave activity thought to be associated with brain deterioration and intellectual impairment[13,14].

Senile dementia is a progressively deteriorating disorder which appears to be caused by one or both of two main diseases: a) vascular dementia (arteriosclerotic dementia, multiple infarct dementia), where there are multiple infarcts with subsequent softening of the brain; b) SDAT (senile dementia of the Alzheimer type) where on post mortem examination of the brain a larger than average quantity of neuritic (senile) plaques and neurofibrillary tangles are found. Brain atrophy can be seen using the computerized tomogram (CT) brain scan which aids diagnosis, but SDAT is reliably diagnosed only post mortem.

The few studies carried out so far with these types of patients[5,16,17] have shown that they have further decrements in SWS, REM sleep and total sleep time if compared with normal elderly, but these studies did not attempt to distinguish between different types of dementia with respect to the EEG patterns and sleep behavior.

The present study investigated aspects of the EEG of wake and sleep in relation to some clinical parameters.

Materials and methods

Ten partly bed-ridden patients from the Geriatric Clinic of the Kantonsspital, Basel, were studied after