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Introduction

Many types of drugs have been found to affect memory processes in laboratory animals. Several of these have been tested in the clinic on patients suffering from memory deficits. For instance, much research interest is presently addressed to the development of 'A memory drug for the aged'.[1] However, much uncertainty exists concerning the aspect(s) of memory affected, the mechanism(s) of action, and the underlying cerebral substrate, whereas more information is of importance for the development of an effective treatment for cognitively impaired patients. The present paper gives a critical discussion of the present state of knowledge on these points. More thorough reviews on the topics discussed will be found elsewhere.[2-5]

On memory and related cognitive functions

Careful neuropsychological research in patients with subjective complaints of failing memory has shown that virtually any kind of lesion in the brain can give rise to memory deficits.[6] These deficits may reflect a 'real' memory disorder, or they may be secondary to another deficit such as an attention deficit, a planning deficit, or slowness. In other words, a memory complaint does not necessarily reflect a memory disorder. Likewise, the performance of animals in tests designed to assess 'learning' and 'memory' depends in part on other cognitive functions such as attention and the state of arousal of the animal.

In man, many different kinds or aspects of memory exist with their own anatomical localizations. For instance, posterior neocortical areas are essential for material/modality specific memory (e.g. memory for faces and for words); the frontal neocortex has a role in the encoding of new information and the retrieval of old memories; the ascending fibre system plays its part in attention and arousal; and diencephalic structures and the hippocampus are important for memory consolidation.[6] Recent neurobiological research on memory processes differentiates 'intrinsic' from 'extrinsic' systems.

It is in the intrinsic system that the information representation develops, probably as a permanent change in synaptic efficiency in large neuronal networks. The extrinsic pathway is the system of pathways that can influence, modulate, or express the information storage but which do not contain memory themselves.[5]

There is much evidence which suggests that the cerebral substrate underlying motor learning is different from that underlying cognitive learning.[7] Consequently, the aspects of human memory and learning studied are different from those in animal studies, as the relative importance of motor learning is much greater in animal experiments than in studies with human subjects.

It will be clear from the foregoing that 'memory' is not a unitary concept: it is better to speak of 'memory processes' and to try to specify the action of different drugs in terms of an action on different aspects of memory.

The pharmacology of memory processes

Acetylcholine Drugs which enhance the availability of endogenous acetylcholine, such as the acetylcholinesterase inhibitor physostygmine, appear to affect the performance of laboratory animals in certain memory tests.[5] Whether there is a facilitation or an impairment of memory depends upon the age of the memory, i.e. the interval between the learning trial ('acquisition') and drug administration. It is presently thought that there must be some optimal level of acetylcholine availability; when this level increases above optimum, a memory impairment is the result. That the effects of acetylcholine antagonists (e.g. scopolamine) are exactly opposite to those of physostygmine is in line with this notion. Besides, scopolamine can induce memory deficits in both monkey and man.

Another line of evidence which implicates acetylcholine in memory processes comes from clinical research: primary degenerative dementia (e.g. Alzheimer's disease) is characterized by memory deficits and by a degeneration of cholinergic fibres ascending to the neocortex.[8] This correlation is not specific for memory functions, as other cognitive deficits are also noted in this disease. Unfortunately, clinical trials which investigated the potential beneficial effects of acetylcholine-enhancing drugs (e.g. physostygmine or the acetylcholine precursors choline or lecithin) have been largely unsuccessful.[1,5] The importance of the memory research performed up till now with cholinergic drugs may thus be the theoretical knowledge it provides: it has been hypothesized that memory consolidation is determined by the activity in cholinergic synapses. Theoretically, these terminals may be part of the intrinsic system (located in the neocortex) in which the information is actually stored, whereas the cell bodies and axones (located subcortically) are part of the extrinsic system.

Catecholamines Although catecholamine agonists and antagonists have an opposite effect on performance in certain memory tests in animals, a depletion of central catecholamines by certain drugs (e.g. reserpine) is not accompanied by amnesia.[5] Those studies which found a correlation between central noradrenaline levels and retention imply stress and an optimal level of arousal more than memory *per se*. Peripheral catecholaminergic pathways also appear to play a physiological role in memory processes. They mediate the peripheral epiphenomena of arousal, and help the organism to be optimally prepared for the adaptation to a changing environment. Interestingly, an improvement in performance appears to be found only in subjects who perform suboptimally. In addition, a dose which is too high may have an adverse effect (McGaugh in reference 5). Such a relationship is reminiscent of the well known U-shaped relationship between arousal and performance.

Taken together, catecholamines seem to be differently involved in memory processes than is acetylcholine. They may be part of the extrinsic system, and underly cognitive functions such as (selective) attention, and they regulate the state of activation/arousal which is an essential prerequisite for memory formation.

Neuropeptides The notion that peptides play a role in memory

processes evolved from the work of de Wied and coworkers.[2,4] Pituitary peptide hormones (adrenocorticotrophic hormone (ACTH), melanocyte-stimulating hormone, vasopressin, β-endorphin) and their fragments appeared to improve performance in several behavioural paradigms, both in intact animals and in animals suffering from experimentally produced amnesia. Peptide fragments devoid of classical endocrine activity shared these behavioural effects. In addition, ever increasing amounts of peptides are discovered in the central nervous system; many other arguments favour the notion that these peptides act directly on the brain. Peptidergic pathways have been found which deliver adrenocorticotrophic hormone, β-endorphin, vasopressin, oxytocin, and their fragments all over the brain, and an intact limbic system appears to be essential for the behavioural activity on memory processes.

An important difference exists between peptides related to the anterior pituitary hormones and those related to the neurohypophysial principles: adrenocorticotrophic hormone-like peptides appear to improve attention/motivation, and to increase electrophysiological arousal via limbic midbrain structures. Their action is short-lasting in contrast to the vasopressins; these peptides have a long-term action (for several days after a single administration), and affect memory consolidation and retrieval (or a process common to both).[2,3] The action of adrenocorticotrophic hormone-like peptides in man seems to be confined to attention, vigilance, and mood; some clinical effect was noted in subjects with senile dementia.[9] The picture concerning the potential clinical relevance of vasopressin is less clear: the beneficial effects of this peptide seem to be clear only in patients who are not characterized by extensive degeneration or lesions in the brain.[3] Effects on mood have been reported for both adrenocorticotrophic hormone and vasopressin. Endorphins also appear to be involved in the modulation of memory processes, but their action is less specific for memory than that of vasopressin. Their effects could be elicited at much lower doses than those needed to induce analgesia.[9]

It is generally acknowledged that neuropeptides and neurohormones act as modulators: their action lasts much longer than the milliseconds for which the classical neurotransmitters exert their effects. In addition, they may act 'at a distance'. Generally, a vast amount of literature suggests that neuropeptides may exert their influence by modulating the synaptic efficacy of the classical neurotransmitters, notably noradrenaline.

Other drugs Some other classes of drugs have been used to influence memory processes in animals and in man. Hydergine is used fairly extensively in the clinic for the treatment of cognitive deficits. Originally a vasodilator, it is now claimed to be a cerebral metabolic enhancer. McDonald,[10] in a recent comparison of all clinical trials performed, stated that effects on cognitive functions were almost certainly secondary to an effect on mood.

Piracetam and the nootropics (γ-aminobutyric acid derivatives) are reported to have a fairly specific effect on memory functions in the laboratory animal but, unfortunately, the clinical findings so far have been very disappointing.[10] Psychostimulants (e.g. caffeine, amphetamine) have an aspecific effect on memory processes, secondary to a general activating effect,[5] and antidepressants may lead to better performance because the decreased speed of information processing in depressed patients is normalized. Finally, protein synthesis inhibitors (e.g. puromycin and cycloheximide) have been used as a tool in memory research.[5] Protein synthesis is essential for permanent information storage, but memory molecules are not formed, as was hypothesized some years ago. It is presently thought that a change in protein synthesis is an important aspect of a chain of biochemical events which leads to the outgrowth of synaptic boutons and spines, the build-up of new synaptic contacts between neurons, and the stabilization of electrical activity in large neuronal networks.[11]

Methodological problems

Both animal and human/clinical studies are often difficult to evaluate because of differences in the terminology used, the interpretations and theories proposed, and differences in important pharmacological parameters.

Type of drug Apart from the different effects which are found with different classes of drugs (acetylcholine, catecholamines, neuropeptides, and other drugs), there are differences between drugs within classes. This is especially true for neuropeptides.[2,3] For instance, minor changes in the amino-acid sequence of these substances can change the activity profile. This is the case for the $ACTH_{4-9}$ analogue which was originally developed as a potentiated congener for the sequence $ACTH_{4-10}$. Animal experiments have shown that the $ACTH_{4-9}$ analogue has an activity profile which suggests that this peptide has an intrinsic new activity. In addition, it has a much longer half-life, and can be administered orally. This compound is presently being tested in clinical trials with patients suffering from senile dementia. Likewise, the neuropeptide desglycinamide[9]-arginine[8]-vasopressin (DGAVP) differs from the vasopressin congeners which are more often used in the clinic. Desamino-D-arginine[8]-vasopressin (DDAVP) and the mother hormone arginine[8]-vasopressin (AVP) have peripheral side-effects on water retention (DDAVP and AVP) and blood pressure (AVP). The agent of choice in clinical trials is therefore DGAVP. Nevertheless, many studies used the other peptides: it may thus be that the effects of DDAVP and AVP are secondary to a perception of bodily changes, such as a normalized urine excretion in diabetes insipidus patients.[3] Besides, the peripheral side-effects prohibit the administration of a higher dosage of the drug. This may prevent a substantial amount of drug from passing through the blood-brain barrier and reaching the site of action in the central nervous system. That small changes within a peptide structure may have profound effects on the behavioural activity has also been shown for other neuropeptides.[2,4] For instance, γ-endorphin and α-endorphin differ in one amino acid but have opposite behavioural effects. Similarly, the behavioural action of $ACTH_{4-10}$ is opposite to that of its D-enantiomer in many behavioural tests (e.g. active and passive avoidance behaviour). Furthermore, the 'ring' structure of vasopressin is thought to affect consolidation, whereas the 'tail' peptide of this hormone may affect retrieval. The intrinsic activity and the pharmacological properties of these peptides may thus be determined by the amino-acid sequence.

Route of administration This is a related parameter which, again, is especially important with respect to the neuropeptides. Generally these substances are rapidly degraded in intestine and blood; therefore, high doses have to be administered to allow access to the central nervous system. This is apparent, for instance, in the case of vasopressin. The amount of this peptide which is needed to elicit behavioural effects in the rat is 20 to 40 times greater after intracerebral administration than after application to specific brain nuclei, and yet 100 to 1000 times more peptide is needed after peripheral administration (de Wied in reference 3). Therefore, future research should focus on peptide congeners which are potentiated, and/or resistant towards metabolic degradation. This is the case for the $ACTH_{4-9}$ analogue. With respect to the vasopressins, DDAVP has a longer half-life than DGAVP, but is behaviourally much less active.

Dose The dose needed to elicit behavioural effects is of paramount importance: acetylcholine and the catecholamines can have different effects at low and high doses, and this is espe-

cially true for the neuropeptides.[2] All of these substances appear to have multiple effects, and the manifestation of these effects depends upon the test parameters chosen and the dose used. Adrenocorticotrophic hormone-like peptides, for instance, affect active and passive avoidance behaviour, positively reinforced behaviour, and sexually motivated behaviour; they induce excessive grooming behaviour in rodents as well as the stretching and yawning syndrome (after central but not after peripheral administration), and induce analgesia (at higher dose levels). In man, effects on vigilance, mood, and social behaviour have been noted. It has been hypothesized that a limited number of basic mechanisms may underly these multiple effects, and that several brain systems are involved in the expression of the different behaviours, depending on the dose and the nature of environmental stimuli.[2] The same is true for other drugs. Endorphins, for example, affect memory processes in low doses and induce analgesia at higher doses. Similarly, AVP affects memory at low doses, but induces barrel rotation behaviour at higher doses (in rodents). Furthermore, the D-isomer of $ACTH_{4-10}$ facilitates passive avoidance behaviour when given at low dose, but impairs the performance at high dose levels. Many other instances can be given.

As pointed out above, similar dose-related effects were found for cholinergic and catecholaminergic drugs. Doses which were too high generally appeared to impair performance. Of course, the time between training and drug administration will affect its effective dose and thus its effect. For instance, an anticholinesterase given prior to retention testing had no effect when the testing was 4 days after learning. It impaired memory after 7 days, and improved memory after 21 days.[5] Likewise, the behavioural effects of vasopressin and adrenocorticotrophic hormone depended upon the time of administration (e.g. after training or before the retention test). Resistance to metabolic degradation, of course, also influences the effective dose level and thus the time period for which such a drug is active.

Theoretical implications

The theories on the mode of action of the drugs mentioned are not mutually exclusive. It becomes evident that cholinergic, catecholaminergic, and peptidergic mechanisms underly the complicated sequence of events that is associated with the selection of new information from the environment, its consolidation, and its retrieval at a later stage. These neurotransmitters and neuromodulators, and the peripheral (stress) hormones probably act together on different stages of the information processing. It can in fact be predicted that many other transmitter substances which have not been investigated up till now will eventually be found to affect memory processes.

Theoretically, the finding that exogenously administered drugs affect memory processes indicates that the endogenous counterparts of these drugs are physiologically involved in these processes. This provides a rationale for the development of drugs which act to enhance decreased levels of endogenous substances. Such a rationale lies behind L-dopa therapy in Parkinsonism and choline therapy in Alzheimer's disease. Likewise, neuropeptide therapy may prove to be of importance in diseases characterized by low endogenous peptide levels.

As discussed above, it may be necessary for several systems to act together for optimal performance. For instance, it is the combination of adrenalectomy and lesioning of the dorsal noradrenaline bundle that impairs performance in rodents.[5] Likewise, exogenously administered vasopressin may not be able to exert any effect in human subjects with extensive lesions in catecholaminergic or cholinergic pathways. The clinical finding that vasopressin-like peptides do not have beneficial effects in patients with extensive brain lesions suggests that the cerebral substrate for the peptide action has been destroyed.[3] Furthermore, the notion that neuropeptides and catecholamines (and also acetylcholine) act together is expressed in the theories that the neuropeptides may act as neuromodulators: they may exert their action by a modulation of the efficacy of other synapses. Neuropeptides such as those derived from adrenocorticotrophic hormone may induce a brain state which is optimal for the selection of relevant information from the environment, the organization of behavioural plans, and the consolidation of the relevant, newly acquired information.[2]

It is of importance to mention the role of stress hormones again. These peripheral hormones and their central counterparts are physiologically involved in the adaptation of the organism to a changing environment. Important aspects of this 'adaptation' can be described in terms of 'learning' and 'memory'. The effects, in animal experiments, of these hormones and their fragments are primarily found in aversively (e.g. shock) motivated tasks. In view of the fact that a stress component can also be found in positively reinforced tasks,[2] the cerebral mechanisms underlying stress (e.g. arousal) seem to play a crucial role in mediating the behavioural effects of the neuropeptides. Several neuropeptides may thus primarily affect performance in man on more or less 'aspecific' aspects of memory, with a secondary effect on memory. The tasks used in the human studies performed up to the present time had their focus on memory *per se*. Indeed the primary effect of the neuropeptides is on other aspects of memory processes, which explains the relative lack of clear-cut peptide effects obtained with objective tests in patients who did report a subjective improvement. Therefore, other tasks may have to be designed in which the emphasis is shifted towards tasks measuring attention processes, activity level, energy, rate of information processing, mood, and so on.

The data discussed so far also imply that it is very important to characterize the nature of the memory deficits in patients who might be treated with the drugs mentioned. A careful neuropsychological investigation will, in addition, provide evidence on the presence of other deficits which might exert an inhibitory effect on the action of the drug.[3]

Conclusions

It will be clear that 'memory' *per se* does not exist. Intrinsic and extrinsic mechanisms exist, and the different aspects of memory depend upon different cerebral substrates. Consequently, different drugs will affect the different types or aspects of memory. We need an integrated view in which information from neuroanatomy, endocrinology, neuropsychology, and neurobiology is used in order to gain insight into the pharmacology of memory.

Such an integrated view is important for the development and use of drugs for the treatment of deficits of memory and other cognitive functions. It will, in addition, enable the collection of more relevant information on the different aspects of memory and the cerebral substrate underlying these cognitive functions.

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