Memory-Enhancing Drugs: A Molecular Perspective

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Abstract: Neurodegenerative diseases associated with dementia are characterized by cognitive deficits and memory impairment, thus stimulating research for memory enhancing drugs. We survey here the state of the art of research and clinical trials on these drugs from cholinesterase inhibitors and drugs acting on neurotransmitter receptors to drugs acting on gene expression.

Key Words: Memory, neurodegenerative disease, acetylcholine, AMPA receptor, CREB, chromatin.

INTRODUCTION

The ability to learn new information and to remember them is a key function of brain working in humans. This ability is shared to various extents, depending on the structural complexity of the nervous system, by our relatives of the animal kingdom and this very important property has been used for better comprehension of the neurobiological basis of memory, as it will be illustrated by many examples in the following paragraphs. Memory is a central component of what we intend when we refer to cognitive functions, together with the other pillars of cognition constituted of problem-solving ability, creativity, imagination, intuition and attention. Cognitive functions tend to be less efficient during aging and they dramatically decline in age-related pathologies involving various degrees of dementia [1]. In most cases, memory impairment is among the first signs of ongoing demented states. This is in particular the case for Alzheimer's disease (AD), the most common and devastating form of dementia, which is going to reach epidemic level (more than 9 million cases forecasted in USA by 2050) after having dramatically increased during the second half of the last century [2]. Typical deficits of memory occurring with aging are mainly related to measurable, albeit mild, defects of declarative memory (i.e. the ability to remember name of persons or past events), which may be due to a decreased speed of brain processes involved in retrieval of information [3]. Mild memory deficits that are below the threshold for a diagnosis of dementia have been differently named as age-associated memory impairment or mild cognitive impairment. While these states are at the borderline between physiology and pathology, they may be considered prodromal to overt dementia and epidemiological studies suggest that individuals affected by these mild forms of memory impairment are subjected to increased risk of developing dementia [4]. From a medical point of view, drugs able to improve cognitive functions and, first of all, memory performances are primarily viewed as tools to ameliorate the conditions of individuals suffering of mild cognitive impairments and dementia patients, including those affected by AD. However, memory enhancers may have a much larger market of potential users, as the mirage of improving normal memory performances is increasingly seducing healthy adult people, who thinks to become able to better cope in this way with the increasing demand for information inherent in modern society. While this way of "doping the mind" [5] is less justified from a medical point of view and surely more questionable for both scientific and ethical reasons, it is easily predicted that it may become more and more popular in the next future. In the present review, we will mainly focus on drugs aimed at targeting specific cognitive processes that are compromised in pathological conditions of dementia and that are, therefore, potential remedies for patients affected by such destructive diseases. In order to better identify the drug targets, a brief summary of the most relevant knowledge regarding the neurobiology of memory will be provided in the next paragraph.

NEUROBIOLOGY OF MEMORY

About 60 years ago, the Canadian neurologist Donald Hebb formulated, for the first time in a conceptually coherent way, the idea that the efficacy of neuron to neuron communication was an activity dependent process and that repeated and strong activation of synaptic connections could result in lasting changes of transmission both in functional and structural terms [6]. A consequence of Hebb's idea was that these modifications of neural circuits were the mechanism through which information could be stored and retrieved by the brain and thus constituted the neural basis of learning and memory. This concept represents the birth date of our present understanding of "synaptic plasticity". Less than a quarter of century later, the concept of Hebbian synapse, i.e. a synapse whose efficacy is dependent on activity, was put on a solid experimental basis by the discovery of Long Term Potentiation (LTP), i.e. the demonstration that a short pulse of high frequency stimulation enhanced synaptic transmission for hours in ex vivo hippocampal slices and for weeks in the hippocampus of intact mammals [7, 8]. In the same hippocampal preparation, as well as in the cerebellum, the theoretically necessary occurrence of mechanisms leading to weakening of synaptic efficacy in selected sets of synapses, i.e a long term depression (LTD) was also demon-

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strated [9, 10]. In parallel, Eric Kandel and his coworkers started their pioneering studies on the much simpler nervous system of the snail *Aplysia californica*, which resulted essential in building the cellular and molecular basis of our present knowledge of synaptic plasticity [11]. A further important contribution came from genetic approaches to the study of learning and memory, which started from the examination of mnemonic effects of mutations in the classic model of the fruit fly *Drosophila melanogaster* [12] and received a great momentum from the introduction of transgenic mice and from the completion of the human genome mapping project.

Memory is the recollection of past events, acquired skills or information and may be entirely conscious in the case of the so-called explicit memory (for instance remembering that you have been in Paris last year or that Paris is the capital of France) or less conscious in the case of implicit memory (for instance automatically remembering how to coordinate motor actions to ride a bike). When a novel experience or information is acquired, it is in the form of short-term memory, which is in many cases temporally labile. Most novel experiences and information are quickly forgotten, but some of them, due to repetition and/or the high emotional impact, are consolidated and give rise to the long-lasting (in some cases permanent) long-term memory, after having passed through an imprecisely-defined stage of intermediate-term memory. In animals, these processes can be studied, experimentally manipulated and quantified by evaluating behavioral responses consequent to learning (for instance how many trials are necessary for a fruit fly or a mice to reach food in an arm of a maze or how strong a freezing response is elicited by re-exposure of a rat to a previously experienced dangerous environmental context) [reviewed by 13-15]. Taking advantage of the previously described models, LTP and LTD in mammalian brain slices and processes of habituation and sensitization occurring in the neural circuits of *Aplysia*, relevant cellular and molecular basis of memory have started to be elucidated during the past two decades. The most essential elements resulting from these studies are summarized below, as they are important to identify potential targets for memory-enhancer drugs. This is a theoretically straightforward way to try to develop novel drugs, as it is based on the dissection of molecular steps that are essential for memory formation and whose malfunctioning may potentially be "cured" by appropriate pharmacological tools. A more traditional approach is represented by the identification of biochemical defects that characterize pathological states in which memory deficits are a major symptom and by the attempt to restore the compromised function. This is, for instance, the case for the several drugs aimed at enhancing the cholinergic activity in demented patients, in particular those affected by AD, as degeneration of the basal forebrain neurons providing cholinergic innervation to the cortex and hippocampus is a well-characterized occurrence in post-mortem brain of demented patients [16-18].

Researches on the biochemical basis of LTP in the hippocampus have allowed to obtain important information regarding the molecular processes sub-serving memory through synaptic plasticity. In a representative synaptic circuit of the hippocampus, the induction of LTP is due to the fact that high frequency stimulation initially activates the AMPA subtype of glutamate receptors, which in turn triggers, through depolarization, the activation of the NMDA-type receptor by releasing the Mg^{++} block of its cationic channel. NMDA receptors thus contribute to further depolarization of the membrane through Na^{+} flux and additionally allow Ca^{++} entry due to the high conductance of the channel for this cation [19]. As elevation of cytosolic Ca^{++} is the pivotal step of subsequent molecular cascades, NMDA receptor acts as a molecular coincidence detector between the presynaptic release of neurotransmitter glutamate and the postsynaptic depolarization necessary to relieve the channel block and to increase Ca^{++} concentration. Calcium is an important second messenger in many cells and in particular in neurons, where it activates signal transduction cascades responsible for the various steps of LTP and plastic synaptic responses. A central role in these cascades is played by protein kinases, starting from two immediate targets of Ca^{++}, the Ca^{++}/calmodulin-dependent type 2 protein kinase (CaMKII) and the protein kinase C (PKC). Another fundamental protein kinase is the cAMP-dependent protein kinase A (PKA), which is necessary in long-term synaptic plasticity from *Aplysia* and *Drosophila* to mammals [20]. Through phosphorylation-dependent activation, pre-existing AMPA receptors sequestrated in cytoplasmic vesicles are incorporated into the postsynaptic membrane, thus increasing synaptic response to released glutamate. This increased postsynaptic response is relatively long-lasting and contributes to the maintenance or "expression" of LTP, with the possible reinforcement caused by the liberation by the postsynaptic neuron of retrograde messenger(s) able to increase the pre-synaptic release of glutamate. In some neural circuits, a bona fide candidate is represented by nitric oxide (NO), a diffusible messenger mainly produced in neurons by the Ca^{++}-dependent enzyme, neuronal nitric oxide synthase (nNOS) [21, 22]. The strict structural and functional coupling between NMDA receptor mediated Ca^{++} entry and NO production has been reviewed elsewhere [23, 24]. The biochemical mechanisms described above account for the induction and maintenance of LTP for a maximum time-span of few hours. Thereafter, functional modification of the circuit responses must rely on changes of gene expression and synthesis of new proteins or altered rate of synthesis/degradation of proteins already present in some amount. This can be easily verified experimentally as inhibition of protein synthesis disrupts late LTP and compromises memory formation [25] A central molecule for late LTP, and therefore a good candidate as a "molecular switch" for long-term memory, is represented by cAMP-responsive element-binding protein (CREB), a leucine-zipper transcription factor that is activated by phosphorylation and regulates the nuclear transcription of many genes, some of which are transcription factors themselves while others are translated into essential proteins promoting cell growth and survival [26-29]. While a complete knowledge of CREB transcriptome is still awaiting, there is no doubt that it is a central regulator of many genes involved in synaptic plasticity [30]. The stimulus-dependent activation of CREB-mediated transcriptional response results in synthesis of proteins that contribute to increase the size and number of synapses, thus constituting the basis for the activity-dependent memory formation derived from the Hebbian concept of synaptic plasticity. The characterization in *Aplysia* of forms of synaptic plasticity, such as

Table 1. Memory-Enhancer Drugs: A Summary

Drug Family	Drug Name	Phase of Study	Reference
AChE inhibitors	Tacrine (Cognex®)	Commercial for AD	[34]
	Donepezil (Aricept®)	Commercial for AD	"
	Rivastigmine(Exelon®)	Commercial for AD	"
	Galantamine (Razadyne®, formerly available as Reminyl®)	Commercial for AD	"
AchRs agonists	Ispronicline	Phase II for AAMI	[44]
	Nefiracetam	Phase II for AD	[56]
NMDA-Rs antagonists	Memantine (Nemenda®)	Commercial for AD	[50]
AMPA-Rs modulators	S-18986-1	Phase II for MCI	[65]
	ORG 24448	Phase II for CDS	[59]
	ORG 26576	Phase II for ADHD	"
	CX 717	Phase II for ADHD, AD	[33]
	CX 1739	Phase I for ADHD, AD	[59]
	CX 516 (Ampalex ®)	Phase II for MCI, AD, FXS & autism, CDS.	[80]
	Piracetam (Nootropil®, Qropi®, Myocalm®, Dinagen®)	Commercial for MCI, AD, DS, CDS.	[69]
	Aniracetam (Draganon®, Ampamet®, Sarple®)	Commercial for MCI	"
	Oxiracetam (Neuromet®)	Commercial for MCI	"
PDE-4 inhibitors	Rolipram	Preclinical phase for MCI	[122]
	MEM 1018	Preclinical phase for MCI	"
	MEM 1091	Preclinical phase for MCI	"
PDE-5 inhibitors	Sildenafil (Viagra®)	Preclinical phase for MCI	[137]
	Vardenafil (Levitra®)	Preclinical phase for MCI	"
	Tadalafil (Cialis®)	Preclinical phase for MCI	"
PKC activators	Bryostatin-1	Phase II for AD	[156]
HDACs inhibitors	SAHA, vorinostat-1 (Zolinza ®)	Preclinical phase for MCI	[185]
	VPA (Depakote®, Depakene®, Convulex®, Stavzor®, Depakine®, Epival®)	Phase III for AD dementia, phase II for CDS, AD, MCI, PTSD and phase I for non-AD dementia.	[186]
	TSA	Preclinical phase for MCI	[185]
	PDX 101, belinostat	Preclinical phase for MCI	"
	MS 275	Preclinical phase for MCI	"
POP inhibitors	JTP-4819	Preclinical phase for MCI and AD dementia	[209]
	ZTTA	Preclinical phase for MCI	[206]
	S-17092	Preclinical phase for MCI	[211]

habituation and sensitization, that share some equivalence with LTD and LTP as well as learning studies in *Drosophila*, have revealed similar biochemical actors and have in particular confirmed the central role of CREB-mediated transcriptional activity [11, 12, 31, 32].

The advances in the knowledge of the molecular and biochemical mechanisms of memory lead to the design of several pharmacological tools that can positively influence the memory processes both in physiological and pathological conditions. The most promising memory-enhancer drugs can

be included in two groups: i) those directed to the initial phase of memory induction and ii) those targeted to the later phase of the signal transduction pathway of memory consolidation. In the first category fall drugs mainly targeted towards compromised neurotransmission. In the second group are mainly comprised drugs that regulate gene expression.

NEUROTRANSMITTER SYSTEMS-RELATED COGNITIVE ENHANCERS

No cure is presently available for most forms of dementia, including AD. Medical treatments are, therefore, symptomatic and many of them are targeted to the most obvious and quantifiable symptom, i.e. decline in cognitive function [33, 34]. As indicated above [16-18], a deficit of cholinergic function in cortical and hippocampal areas, due to degeneration of the projection neurons located in the basal forebrain, is a common occurrence in post-mortem brains of AD patients. It was initially believed that the cholinergic deficit was a relatively early symptom in the disease progression and, therefore, a good target for drugs aimed at slowing down the progression itself. On this rationale, several drugs targeted to enhance the activity of the cholinergic transmission were introduced in the pre-clinical testing and, then, in the clinical practice. More recent evidence, however, indicates that a significant cholinergic deficit is not a characteristic feature of prodromal and early stages of Alzheimer's dementia, but rather a relatively later-occurring event [35-37] and this may explain the limited success of cholinergic transmission-targeted therapies. To compensate for the lower synthesis of acetylcholine and its decreased availability at the synapses, inhibitors of cholinesterases, the enzymes responsible for acetylcholine hydrolysis in the synaptic cleft, were tested in several trials and introduced as standard care for patients, in particular those diagnosed as suffering of mild to intermediate forms of AD on the basis of their score in Mini-Mental State Examination [38]. Of the four cholinesterase inhibitors approved by US Food and Drug Administration (FDA), tacrine, donepezil, rivastigmine and galantamine, the latter three have been in particular extensively used for their low level of adverse side effects. Main results obtained have been recently reviewed for a number of clinical trials carried on for periods of up to 6 months with standard drug dosages [38-40]. Moderate beneficial effects were evaluated in most of these studies in terms of slowing down the decline rate of cognitive functions, improving global clinical state and some behavioral activities, in particular those related to daily living. A significant, but acceptable, level of adverse side effects was associated with treatments and, in a comparative study, donepezil gave less side effects than rivastigmine. While some concerns have been raised regarding possible influence of cholinesterase inhibitor treatments on mortality, a recent retrospective cohort study has denied that long-term (more than 2 years-long) treatment with donezepil and galantamine are a significant factor of risk for mortality of AD patients [41]. In general, the moderate positive effects of treatments were better evident in cases of mild to moderate dementia, as compared to advanced dementia stages, and in cases of absence of gaps in the intake of drugs during the treatment [38-40]. As efficacy of treatments appears to be inversely correlated with the stage of dementia at the time of treatment starting, it is interesting to know whether administration at prodromal stages of AD is able to prevent, or at least delay, the onset of the diagnosed dementia. However, a recent survey of both published and unpublished data from several clinical trials based on long-term administration of donezepil, rivastigmine and galantamine to patients diagnosed with Mild Cognitive Impairment (MCI), a potential factor of risk for AD, reached negative conclusions [42]. No evidence was found from this study that cholinesterase inhibitors could improve cognitive ability of patients nor reduce the risk or delay the onset for AD and that, therefore, adverse side effects prevailed over possible benefits. This negative result is not surprising in view of the fact that, contrary to what believed until recently, MCI is not characterized by a patent cholinergic deficit [36, 37]. In conclusion, surveys on clinical trials suggest that treatments with cholinesterase inhibitors maintain a definite therapeutic value in moderately improving memory performances and daily life of patients, in particular those suffering of mild to intermediate forms of dementia. The possibility, however, to use this therapeutic approach to counteract, or at least to delay, the insurgency of dementia, starting treatments on early appearance of symptoms that may be judged prodromal to dementia, does not seem to be founded on solid ground.

Alternative ways to target the cholinergic system to improve memory in dementia is to use drugs able to increase the activity of cholinergic transmission, by acting at the neurotransmitter receptor level. Some evidence for a favorable role of nicotine on memory, in particular on patients suffering neuropsychiatric disorders [43], has targeted research towards agonists of nicotinic subtypes of brain acetylcholine receptors. In particular, agonists of the $\alpha4\beta2$ nicotinic receptor (Isopronicline) and of the $\alpha7$ nicotinic receptor have proved to enhance memory in animal studies and to be well tolerated by human subjects, so that they are currently tested in clinical trials with some preliminary encouraging results [44, 45]. Muscarinic agonists may also contribute to improvement of cognitive function, as it may be inferred from animal studies, in which they seem to improve the efficacy of AChE inhibitors and also to act through interference with other neurotransmitter systems (glutamatergic, GABAergic and monoaminergic) [46-48]. Some potentially interesting ways to improve cognitive functions in several pathological states, including dementia, through combined targeting of the cholinergic and the monoaminergic systems, have been recently reviewed [2, 5].

Due to the above mentioned involvement in models of synaptic plasticity such as LTP, ionotropic glutamatergic receptors, both of the NMDA and non-NMDA subtypes, have been taken into account as potential targets for memory enhancing drugs. Regarding NMDA receptor, memantine is the most-used approved drug which is often prescribed in conjunction with AChE inhibitor therapy [49, 50]. This drug is a low-affinity reversible antagonist of the NMDA receptor that may counteract the excessive background activity of the receptor, occurring with age and development of dementia, without negatively affecting the normal receptor function required for cognition [51-53]. Results from clinical trials gave some support to use of memantine in dementia, as they have indicated a favorable effect in memory improvement in

early stages of AD [54]. The concept of combination therapy for dementia has been strengthened by the demonstration that the most recently introduced AChE inhibitor, galantamine, also acts as agonist of nicotinic receptor subtypes [55], thus allowing better association between the NMDA receptor activity control, ensured by memantine, and the potentiation of cholinergic transmission. Potentially interesting perspectives of these association therapies are given by the effect of other so-called nootropic drugs such as nefiracetam, which selectively potentiates the activity of α4β2 nicotinic receptor [56].

The AMPA subtype receptor plays an essential role in LTP and is, therefore, a candidate target for drugs aimed at enhancing memory performance and cognition. Indeed, the regulation of the AMPA-type glutamate receptors (AMPARs) is a highly dynamic process and is a crucial mechanism for memory. In particular, it has been demonstrated that synaptic transmission *via* AMPA receptors is required not only for memory formation, but also for consolidation and retrieval [reviewed by 57, 58]. Therefore, drugs acting on AMPA receptors have been extensively studied to find potential memory-enhancers and several companies (Cortex, Lilly, Organon, Servier) are striving to produce AMPA receptor-based memory drugs [59]. Initially, several compounds of the class of thiazides have been identified as positive modulators of AMPA receptors and, therefore, potential memory enhancers, but they are not able to pass the blood-brain barrier. To overcome this problem, several thiazide derivatives have been produced; among them: 7-Chloro-3-methyl-3-4-dihydro-2H-1,2,4 benzothiadiazine S,S-dioxide (IDRA 21) [60] and 1-(1,3-benzodioxol-5-ylcarbonyl)-piperidine (1-BCP) [61-63], which are currently at a preclinical phase of study, and (S)-2,3-dihydro-[3,4]cyclopentano-1,2,4-benzothiadiazine-1,1-dioxide (S-18986-1), which is in the clinical phase I status [64, 65].

Both 1-BCP and S-18986-1 belong to the "ampakines", a family of AMPA receptor modulators developed by Cortex Pharmaceuticals. Other ampakines that are presently under clinical trial are ORG24448, ORG26576, CX717 (Phase II) and CX1739 (Phase I). Ampakines were the first allosteric modulators of AMPA receptors able to augment excitatory transmission in brain. They have no direct agonist or antagonist actions but, instead, they modify two aspects of receptor biophysics, desensitization and deactivation, that terminate the synaptic current [61, 66]. By slowing down these two processes, ampakines enhance and prolong the synaptic currents generated by release of glutamate from axon terminals. These drugs freely enter the brain, where they potentiate both glutamatergic transmission and the activity of cortical neurons controlling complex behaviors [67-69]. Being modulators, ampakines only affect those AMPA receptors activated by endogenously released transmitter and thus only those networks already engaged in brain activity. This feature, coupled with the absence of targets outside the central nervous system, presumably accounts for their positive effects on memory at dosages well below those producing side-effects, such as seizures [68]. Ampakine compounds, like CX614 and CX929, bind to the well-characterized cyclothiazide binding site of the AMPA receptors and are referred as high-impact compounds. In contrast, compounds like CX717, CX701, ORG24448 and ORG26576 bind to a different modulatory site on the AMPA receptor complex and are identified as low-impact compounds. Both types of drugs positively modulate the AMPA receptor function, but in a different way: low-impact compounds increase the amplitude of the neuronal synaptic potential, while the high-impact compounds generally increase both the amplitude and the half-width of the neuronal synaptic potential [70]. Additionally, the high-impact compounds activate the expression of certain genes in the neuron, including neurotrophins such as Brain Derived Neurotrophic Factor (BDNF). Changes in synaptic potency, due to both CX614 and CX546, produce network activity effects sufficient to induce neurotrophin genes and raise the possibility to use positive AMPA modulators for neuroprotection and memory enhancement, through elevation of the endogenous neurotrophin levels [71-73]. More recently, it has been suggested that ampakine ability to induce neurotrophin expression could be of therapeutic value in the treatment of Rett's syndrome too [74].

From the chemical point of view, most of the ampakines are benzoylpyrrolidines. 1-(quinoxalin-6-ylcarbonyl) piperidine: PBD-12, also known as CX516 is one of these drugs. In rats, this drug facilitates olfactory learning [75] and memory encoding in several other paradigms [76], by increasing fast excitatory glutamatergic synaptic responses [66]. In humans, it improves delayed recall in aged individuals [77] and it enhances memory encoding based on tests of visual recognition, motor performance, and general intellectual activity [78]. Interestingly, an interaction between the ampakine CX-516 and low doses of different antipsychotics has been noticed, that is generally additive and sometimes synergistic [79]. Therefore, CX-516 (Ampalex®) is in phase II clinical trial for the potential treatment of MCI, AD, schizophrenia and ADHD [80]. CX-546 was the second drug of interest generated by the Cortex research program. It was an improvement over CX-516 in some respects, but had problems with limited oral bioavailability. However, CX-546 still represented a significant advancement that led to the development of newer compounds, such as CX-614 and CX-717, with superior properties over the earlier drugs. The ampakine CX-717, in addition of enhancing cognitive performance under normal alert conditions, also proved to be effective in alleviating impairment of performance due to sleep deprivation in monkeys, but not in humans [81, 82].

Beside the ampakines, several other AMPA modulators exert a positive effect on memory. One class of pyrrolidone-derived drugs (2-oxopyrrolidine), such as aniracetam and piracetam, has been the subject of research for more than three decades [83, 84]. These drugs are known as "nootropic" agents, as they exert a cognitive-enhancer effect. Accordingly, early experimental and clinical work focused on their nootropic effects, while later their properties as stroke neuroprotective and antiepileptic agents were investigated [84]. Piracetam, the first member of the class, was developed in the early '70s by pioneering research by Giurgea [85], who coined the term "nootropic". Piracetam was also the first nootropic drug to reach the clinical practice since the early '70s [86]. These drugs are able to reverse amnesia induced by electroconvulsive shock [87], to counteract the memory dysfunctions in depressed [88] and schizophrenic patients

[89] as well as in children with dyslexia [90]. In patients with AD, only long-term and high-dose piracetam treatment slows the progression of cognitive deterioration [91-93]. These findings suggest that nootropics could influence a common mechanism underlying the amnesias. However, piracetam therapy did not significantly improve cognitive performance in children with Down's syndrome and was instead associated with central nervous system adverse stimulatory effects [94]. Piracetam has a rapid onset of action on behavioral variables in psychiatric patients, but its therapeutic effect tends to diminish with time, possibly as the result of overstimulation [95]. In rats, piracetam facilitates memory retrieval, but it doesn't impair extinction [96]. On the other hand, it fails to facilitate acquisition or retention in aged rats [97]. Piracetam overcomes the amnesic effect of scopolamine, diazepam and electroconvulsive shock [98] mainly by acting on hippocampus [99]. Biochemically, it increases the peak amplitude and reduces the rate of decay of the ion current generated through AMPA receptors, enhances the stimulation of Ca^{++} influx specifically produced by the same receptors and increases the maximal density of AMPA binding sites in synaptic membranes [100]. Therefore, positive modulation of AMPA receptors by piracetam provides the molecular substrate which explains the clinical efficacy of nootropic drugs as memory-enhancers. Moreover, it increases muscarinic cholinergic receptor density in the frontal cortex of aged but not of young mice [101] and, in general, it activates the cholinergic system [102]. In agreement with this mechanism of action, the combined effect of choline and piracetam achieved substantial efficacy in aging [103, 104].

Aniracetam (Ro 13-5057, 1-anisoyl-2-pyrrolidinone) was known to improve cognitive functions which are impaired by different experimental procedures and in different phases of the learning and memory process since the early '80s [105]. However, only in '90s it has been demonstrated that aniracetam acts on memory through AMPA receptor modulation [106-108]. Aniracetam increases the currents mediated by AMPA receptors through a reduction in their desensitization and an increase in conductance, thus resulting in facilitation of LTP [109]. However, aniracetam action seems to be not solely mediated through modification of excitation, but also through enhanced cortical GABAergic inhibition, which could explain the antidepressant effect of the drug [110, 111]. Both aniracetam and oxiracetam reversed the learning impairment in rodents [112, 113]. Results from trials in elderly patients with mild to moderate cognitive impairment due to senile dementia of the Alzheimer type, suggest that aniracetam is of benefit, but conclusive evidence has not been reached yet [114- 116].

The diazoxide derivative IDRA-21 is a cogener of aniracetam, as they are both negative allosteric modulator of glutamate-induced AMPA receptor desensitization. IDRA-21 attenuates the rapid auto-desensitization of AMPA receptors and increases excitatory synaptic strength [117], facilitates LTP in hippocampal slices [66], improves cognition, as revealed by water maze and passive avoidance tests in rats [60] and improves the cognitive performances of a delayed matching-to-sample task by young adult and, to a lower extent, aged rhesus monkeys [118]. These findings support the use of AMPA modulators like IDRA-21 in the treatment of cognitive/memory disorders, in particular those associated with aging.

DRUGS THAT IMPROVE MEMORY CONSOLIDATION ACTING ON GENE EXPRESSION

The second group of memory-enhancer drugs are those directed to strengthen memory consolidation mainly acting on gene expression. In particular, the transcription factor CREB has been shown to be a key control-point in memory consolidation, as its loss of function determines an impairment in long-term, but not short-term memory and an increase in its activity enhances long-term memory formation without affecting the short-term one. Therefore, CREB is now considered the "molecular switch" to produce the memory consolidation and, therefore, an ideal molecular target for drug discovery. Starting from this, several companies, such as Helicon Therapeutics, have been directed to identify drug compounds that enhance memory formation *via* augmentation of CREB level and activity [119-121]. The regulation of CREB-dependent gene expression can be exerted by two main mechanisms. The first approach acts directly through CREB phosphorylation [121] and it is mainly due to an increase in the level of second messengers, such as cAMP and cGMP [122]. The second is an indirect mechanisms that regulate gene expression through chromatin remodeling, in particular though histone acetylation.

Regarding the possibility to regulate CREB phosphorylation, a valuable target is represented by phosphodiesterases (PDE) [122]. This is in agreement with the knowledge of the molecular mechanisms of memory consolidation, as inhibition of PDE activity leads to an increase in cAMP or cGMP level and, consequently, in protein kinases activity, which in turn drives to CREB phosphorylation and activation. Eleven PDE families, comprised of more than 50 distinct members have been so far identified, but only PDE2, PDE4 and PDE5 have been demonstrated to be candidate targets for memory improvement. These PDEs differ for the substrate that they target, i.e. cAMP or cGMP [reviewed by 123]. Depending from the substrate, these PDEs are involved in different phase of memory: PDE4 (cAMP) is mainly involved in acquisition processes, although a possible role in late consolidation processes cannot be excluded, PDE5 (cGMP) in early consolidation processes, while PDE2 inhibitors may improve both memory processes, since PDE2 inhibition affects both cAMP and cGMP levels [124-126].

The prototypic PDE4 inhibitor is rolipram, which determines an increase in cAMP levels and, in turn, PKA activation. PKA has been widely considered a good therapeutic target for memory disorders, as its activation leads to CREB phosphorylation and, therefore, CREB-dependent gene transcription [20]. Since the '80s, rolipram has been shown to reverse amnesia [127] but it has been later demonstrated that in animal models it facilitates memory establishment in both physiological and pathological conditions, by elevating CREB phosphorylation [127-133]. Interestingly, rolipram exhibits also an antipsychotic activity [134] and it is under phase II clinical trial as anti-depressive treatment. Other PDE4 inhibitors, such as MEM1018 and MEM1091, have been shown to enhance memory in a way similar to rolipram [135].

Another group of PDE inhibitors that are currently studied as memory-enhancers are those targeted to PDE5 [136]. PDE5 is an enzyme that specifically hydrolyzes cGMP [137], a second messenger produced by guanylate cyclase which is mainly regulated by the diffusible messenger nitric oxide. This signal transduction pathway is involved in memory and its dysfunction in cognition deficits [138, 139]. For many years, nonselective PDE5 inhibitors such as caffeine, theophylline and IBMX have been used, however several specific PDE5 inhibitors have been recently discovered [140]. Reported PDE5 inhibitors can be divided into the following classes: i) cGMP-based, represented by sildenafil (Viagra) and vardenafil (Levitra) (Pfizer, Bayer, Sheering-Plough), ii) β-carboline-derived, represented by tadalafil (Cialis) (Lilly, Johnson&Johnson), iii) quinazoline and isoquinolinone derivatives (Bristol-Myers-Squibb [BMS], Japan), and iv) phthalazine derivatives (BMS, Japan). Among them, only the most potent PDE5 inhibitors have clearly reported to have a memory-enhancer effect [137]. In fact, both sildenafil and vardenafil have been shown to improve memory consolidation in rodents by inhibiting PDE5 and therefore increasing cGMP levels, without any effect on memory formation [141-143]. Sildenafil, as well as the PDE4 inhibitor rolipram, has a positive effect on memory retrieval in monkeys [144]. Moreover, it reduces memory impairment due to hyperammonemia [145, 146] and NOS inhibition [147]. Interestingly, sildenafil exerts also an anti-depressive effect [148] and neuroprotection against stroke [149, 150] and ischemia [151]. For both effects it is presently under phase I clinical trials.

Downstream the second messengers, another target for memory-enhancer drugs are the protein kinase pathways and, among them, the most interesting for a therapeutic approach is the protein kinase C. PKC plays a critical role in synaptic plasticity and in various types of learning and memory [152-154]. In addition, PKC signaling alteration is associated with cognitive deficits in aging, AD and following stroke. In preclinical studies, an appropriate activation of PKC isozymes has been found to enhance learning and memory and to contrast dementia and neurodegeneration in several models [reviewed 155-157]. Among PKC activators, bryostatin-1 is particularly interesting. It is a powerful drug, which activates PKC at nanomolar concentration. Its anti-oncogenic effect is widely recognized [158, 159], but more recently it has been proposed to exert also a cognitive-enhancer effect [reviewed by 160], in both physiological and pathological conditions [161-164]. Presently, bryostatin-1 is under phase II clinical trial for mild AD.

Gene expression, including CREB-dependent gene expression, can be indirectly regulated through epigenetic mechanisms, mainly histone acetylation. Chromatin remodeling is widely recognized as a fundamental mechanism of neuronal gene-expression regulation. In fact, to permit gene expression chromatin needs to be unpacked in order to expose regulatory sequences to transcription factors [reviewed by 165, 166]. The main mechanism to regulate chromatin state is through histone post-translational modifications, especially acetylation. The balance between histone acetyltransferase (HAT) and histone deacetylase (HDAC) activity determines the level of histone acetylation, the chromatin state and, consequently, the transcriptional activity. Therefore, the enzymatic system that control histone acetylation is the most interesting target for pharmacological tools targeted to epigenetically regulate gene expression [167-169]. To activate gene expression in long-term memory, CREB needs the coactivator CREB Binding Protein (CBP) which possesses a HAT activity that is necessary to stimulate transcription [170, 171]. CBP-HAT activity has been assessed to be a critical component of memory consolidation and its impairment determines cognitive deficits, for example in Rubinstein-Taybi syndrome (RTS) [131, 172-175]. In general, an increase in histone acetylation level is required for learning and memory, but the role of the HDACs is still unclear [176-180]. Notwithstanding this, one of the most powerful and promising approach for the pharmacological enhancement of memory is through HDACs inhibition. Several HDAC inhibitors are known, some of them are under clinical trial for their therapeutic use against cancer and one, vorinostat 1 (SAHA, Zolinza®, Merck), has been approved in 2006 by US FDA for cutaneous T-cell lymphoma (CTCL). From the chemical point of view, they can be divided in 4 classes: i) small chain fatty acid and derivatives, such as sodium butyrate, phenylbutyrate and valproic acid; ii) hydroxamate small molecule inhibitors, such as trichostatin A (TSA), suberoylanilide hydroxamic acid (SAHA) and PDX-101; iii) non-hydroxamate small molecule inhibitors, as MS-275; iv) cyclic peptides, as despeptide and apicidin [reviewed by 181-183]. Of these classes, the most studied for their potential effect on brain function are the small chain fatty acids, because they are well-known to cross the blood-brain barrier [reviewed by 184].

Phenylbutyrate is under phase II clinical trial for its neuroprotective effect in Huntington's disease (HD) and amyotrophic lateral sclerosis (ALS), but it is at a pre-clinical stage as a cognitive enhancer. In fact, sodium butyrate, as well as trichostatin A (TSA), enhance formation of long-term memory, by increasing histone acetylation, sprouting of dendrites and number of synapses [177, 178], and facilitate extinction [185].

Valproic acid (VPA, Depakote®) is an FDA appoved anti-seizure drug and it is at phase II in different clinical trials as neuroprotective agent against HD, ALS, Spinal Muscular Atrophy and Progressive Supranuclear Palsy. In fact, the neuroprotective effect of VPA has been widely demonstrated in several pre-clinical models of neurodegeneration [reviewed by 186]. Moreover, VPA is at phase III clinical trial for the treatment of dementia in AD and at phase I for other dementia. The VPA effect on cognition is known from the '90s, when it has been demonstrated in epileptic patients [187]. Later, it has been discovered a more general memory enhancer effect of this drug [179, 188-190].

OTHER DRUGS

Among the drugs acting on memory neither through the neurotransmitter system nor by regulating gene expression, there are the inhibitors of Prolyl OligoPeptidases (POPs). These drugs have been demonstrated to be nootropic agents since late 80's [191]. POPs are ubiquitous post-proline cleaving enzymes that hydrolyse peptide bonds mainly at the carboxyl site of l-proline. In mammals, POPs are the most

abundant among brain peptidases. The exact function of these enzymes remains unclear, but it has been shown that POPs participate in several aspects of brain function including learning, memory and mood, most probably through interference with inositol cycle [192-194]. Moreover, several reports associate POPs with various neurological disorders, such as neuropsychiatric diseases [195, 196], AD [195-200] and PD [201-203]. POP inhibitors have been shown to have a positive effect on learning, memory and memory-related behavior. Indeed, several POP inhibitors, such as JTP-4819, ZTTA and S17092-1, reverse memory loss in animal models of drug- or lesion-induced amnesia, in aging and in models of neurodegenerative diseases [204-209]. Several POP inhibitors have already been evaluated in preclinical trials as potential drugs for the treatment of natural memory deficits that occur with aging, as well as of the pathological memory loss characteristic of AD [reviewed by 196, 200, 209] and clinical studies for some of these compounds are on-going [210-211].

CONCLUSION

The present survey highlights the state of the art of research aimed at finding and testing drugs potentially able to counteract the mild memory impairment occurring with aging, as well as the much more dramatic condition of cognitive dysfunction occurring in diseases characterized by dementia. Most used drugs for mild forms of dementia and AD are cholinesterase inhibitors. A relatively large mess of data confirms that this therapeutic approach results in limited, even if valuable, benefit to patients. It is however clear that potential developments of this class of drugs are not very much promising, based on the results of clinical practice as well as on the better knowledge presently available on the neurobiology of memory. Potentially more promising are drugs specifically acting on some specific step of initial memory formation, in particular those interacting with synaptic receptors known to play an important role in memory. Ampakines are probably the most interesting candidates among these drugs, mainly because they essentially act as enhancers of "natural" activation of neural circuits involved in memory formation. Regarding the essential step of memory consolidation, there is little doubt that future approach will be mainly based on manipulation of gene expression by nervous cells, based on the extensive knowledge already obtained on the central role of this mechanism in long term mnemonic and cognitive processes. We outline here the main results so far obtained by research aimed at enhancing the activity of the transcription factor CREB which is now recognized to play a role of "molecular switch" in memory, as well as at regulating transcriptional activity through epigenetic mechanisms, mainly based on the control of the acetylation state of histones. While it is probably too early to predict the future outcome of this research, in particular regarding possible therapeutic relevance, its potential seems to be very well founded on the mainstream of recent acquisitions on the molecular mechanisms involved in memory and cognition. It is also relevant to stress that enhancing CREB transcriptional activity in neurons, for instance through phosphodiesterase inhibitors, and increasing histone acetylation, for instance through histone deacetylase inhibitors, also results in a general pattern of gene expression favoring neuron survival and stimulating neuroprotection. This property will hopefully result very important for perspective treatment of those diseases in which dementia is associated with neurodegeneration caused by lack of pro survival factors.

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ABBREVIATIONS

AAMI	=	Aging Associated Memory Impairment.
AChE	=	Acetyl Choline Esterase
AD	=	Alzheimer's Disease.
ADHD	=	Attention Deficit Hyperactivity Disorder
ALS	=	Amyotrophic Lateral Sclerosis
AMPA	=	alpha-Amino-3-hydroxy-5-Methyl-4-isoxazolePropionic Acid
AMPARs	=	AMPA-type glutamate Receptors
BDNF	=	Brain Derived Neurotrophic Factor
CAMKII	=	Ca^{++}/calmodulin-dependent type 2 Protein Kinase
cAMP	=	cyclic Adenosine MonoPhosphate
CBP	=	CREB Binding Protein
CDS	=	Cognitive Deficits in Schizophrenia
cGMP	=	cyclic Guanosine MonoPhosphate
CREB	=	cAMP-Responsive Element-Binding protein
FDA	=	Food and Drug Administration
FXS	=	Fragile X Syndrome
GABA	=	Gamma-AminoButyric Acid
HAT	=	Histone Acetyl-Transferase
HD	=	Huntington's Disease
HDAC	=	Histone DeACetylase
LTD	=	Long Term Depression
LTP	=	Long Term Potentiation
MCI	=	Mild Cognitive Impairment
NMDA	=	N-methyl-D-aspartic acid
nNOS	=	neuronal Nitric Oxide Synthase
NO	=	Nitric Oxide
PDE	=	PhosphoDiEsterase
PKA	=	cAMP-dependent Protein Kinase
PKC	=	Protein Kinase C
POP	=	Prolyl OligoPeptidases

PTSD = Post-Traumatic Stress Disorder

RTS = Rubinstein-Taybi syndrome

SAHA = SuberoylAnilide Hydroxamic Acid

TSA = TrichoStatin A

VPA = Valproic Acid

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