

Impaired cognition and attention in adults: pharmacological management strategies

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Abstract: Cognitive psychology has provided clinicians with specific tools for analyzing the processes of cognition (memory, language) and executive functions (attention-concentration, abstract reasoning, planning). Neuropsychology, coupled with the neurosciences (including neuroimaging techniques), has authenticated the existence of early disorders affecting the “superior or intellectual” functions of the human brain. The prevalence of cognitive and attention disorders is high in adults because all the diseases implicating the central nervous system are associated with cognitive correlates of variable intensity depending on the disease process and the age of the patient. In some pathologies, cognitive impairment can be a leading symptom such as in schizophrenia, posttraumatic stress disorder or an emblematic stigmata as in dementia including Alzheimer’s disease. Paradoxically, public health authorities have only recognized as medications for improving cognitive symptoms those with proven efficacy in the symptomatic treatment of patients with Alzheimer’s disease; the other cognitive impairments are relegated to the orphanage of syndromes and symptoms dispossessed of medication. The purpose of this review is to promote a true “pharmacology of cognition” based on the recent knowledge in neurosciences. Data from adult human beings, mainly concerning memory, language, and attention processes, will be reported. “Drug therapeutic strategies” for improving cognition (except for memory function) are currently rather scarce, but promising perspectives for a new neurobiological approach to cognitive pharmacology will be highlighted.

Keywords: cognitive disorders, attention, memory, pharmacology, treatment, pharmacovigilance, dementia.

Introduction

In human beings, cognitive functions correspond schematically to the brain processes of acquisition and exploitation of knowledge. Research in cognitive psychology and neurosciences is devoted to unraveling these complex processes that underlie several mental functions. The focus has been put on the analysis of what used to be called “superior functions” such as language, memory or decision-making because of their important role in thought and communication between individuals. The high prevalence of cognitive complaints has prompted neuropsychologists to elaborate tools necessary for the objective measurement and understanding of cognitive alterations, thereby allowing the establishment of a diagnosis. Thus, in the clinical setting, cognitive impairment corresponds to a symptom (eg, amnesia), a combination of symptoms defining a recognized syndrome (eg, amnesic syndrome) or a specific disease (eg, Alzheimer’s disease [AD]). Each nosographic entity is described by a set of criteria defining alterations in memory (Tulving 1985; De Deyn et al 2003; Lieury 2005), language (Damasio and Damasio 1992; Damasio et al 1996; Damasio 1997; Frederici 2000; Fries et al 2003), and executive functions, which also include concentration, or more precisely attention (Berger and Posner 2000; Cowan et al 2005) necessary for planning, organization, and synchronization of complex actions (Stuss et al 1995; Stuss and Alexander 2000; Royall et al 2002).

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Cognitive impairment, explicitly demonstrated by altered performance in specific tasks, is of high prevalence as it is associated with advanced age (Raz 2000) and most neurological and psychiatric disorders. As a rule, the impairment affects several domains of cognition (memories, executive functions, attention, etc) simultaneously or consecutively (eg, isolated memory impairment converting into AD). It can develop progressively (neurodegenerative diseases) or occur suddenly after an acute event (stroke, head trauma).

The severity of the cognitive impairment is often in the forefront of a major clinical presentation like in dementia (Geschwind et al 2001; Pachana et al 1996), Attention-Deficit-Hyperactivity Disorder (ADHD) (Elia et al 1999), schizophrenia (Kuperberg and Heckers 2000; Aleman et al 1999; Heinrichs and Zakzanis 1998), or Parkinson's disease (PD) (Boyle et al 2005; Fernandez et al 2005). Cognitive impairment thus occurs in very different contexts involving the central nervous system (CNS) and resulting from very different pathogenic processes (neurodegeneration, inflammation, toxic reaction, ischemia, trauma, neurochemical deficiency) (Budson and Price 2005). This has logically led to a new domain of pharmaceutical research, "cognitive pharmacology", and, with recent advances in neurobiology, the emergence of new therapeutic perspectives for improving altered cognitive functions (Table 1).

Table 1 Main cognitive disorders

Orientation
Attention/Concentration/Distractibility
Overload-Breakdown of comprehension
Memories
Reasoning and problem solving
Organizational skills
Rate of processing
Perseverance
Motivation/initiation

The purpose of this review is to highlight potential drugs, and therefore therapeutic drug strategies for improving cognitive impairment in adults. Arguments are also put forward favoring more extensive indications for pharmacological management of a wider range of pathological conditions involving cognitive dysfunction; this will broaden the scope of patients benefiting from advances in cognitive pharmacology and neurosciences, as strongly suggested by the 2nd Canadian Conference on Antidementia Drugs (Feldman et al 2006).

The biological basis of cognition

Although the biological and neurochemical basis of human cognition is undeniable (Ichols and Newsome 1999), human thought is something more than the result of a chemical secretion of the brain. Cognition is a complex phenomenon involving multiple levels of neurobiological processes. Very schematically, studies are thus designed to search for a correlation between a given task requiring cognitive work and an observable elementary change within the CNS. Access to specific modules of cognition, particularly memory (Lynch 2002; Arshavsky 2003; Drapeau et al 2003; Nader 2003) and attention (Coull 1998; Filley 2002; Russell et al 2005), can be facilitated with animal models, mainly in rodents and primates, whereas language and linguistics are strictly limited to human research (Perani et al 1999; Pulvermuller 1999).

Functional anatomy

Functional neuroimaging using positron emission tomography (PET), functional nuclear magnetic resonance (fMRI), magnetoencephalography (MEG) or magnetic resonance spectroscopy (Ross and Sachdev 2004) has greatly contributed to our knowledge of the anatomic substrate of the principal cognitive functions. The hippocampus is involved in detecting and encoding new information and the striato-frontal circuits in decision making processes while the frontal lobe is involved the contextual retrieval and in the shift from one idea or one task to another. Long-term memory and its storage are scattered over different areas of the cerebral cortex (Woolf 1998); this notion of distributed anatomic localizations contrasts with the localized areas described by phrenology. A bilingual person, for example, has distinct and separate temporal cortical areas handling each separate language, passage from one to the other activating the Broca area and spelling and phonology activating the supramarginalis gyrus (Price et al 1999). Attentional processes also involve a substratum of complex networks regulating and maintaining alertness and orienting sensorial information and executive control (Fan and Posner 2004; Filley 2002; Fernandez-Duque and Posner 2001).

Knowledge of the functional substratum in the human brain is particularly important in neuropsychology. Zhang and Feng (1999) reported particularly illustrative work demonstrating that analysis of Chinese characters with their fundamental attributes (pictographic similarity, homophony, synonymia) involves close collaboration between the two cerebral hemispheres, probably via the corpus callosum.

Histological modifications (eg, change in synaptic density) associated with cognitive performance or learning have been indirectly demonstrated with MEG in elite cello players compared to music lovers or to controls without music training (Pantev et al 1998). This very partial list offers a few arguments favoring a distributed anatomy of cognition (cross-talks between these structures).

Neurochemistry

Neurochemistry, although difficult to measure in humans, provides clear proof of the organic nature of cognition, offering attractive targets for designing new compounds. Technological advances, eg, specific ligands with PET-scan, experimental models in rodents or primates, in vivo access to neurotransmitters, cerebral metabolism etc, are crucial for targeting drugs to correct for neurochemical anomalies. All of these techniques have their specific limitations and uncertainties explaining why only a few cognitive functions (memory, orientation, attention, decision making, speed of data processing, learning) and rare neurotransmission systems (acetylcholine [ACh], dopamine [DA], GABA, glutamate) and their respective receptors are accessible in humans. Consequently, cognitive pharmacology is limited at the present time to drugs affecting the aminergic (antipsychotics, antiparkinsonians, psychostimulants, drugs such as cocaine), GABAergic (anxiolytics), and cholinergic (cholinesterase inhibitors, nicotine agonists) systems and substances activating neuronal metabolism (nootropic agents, vasodilators and brain oxygenators) (Lynch 2002; Lockhart and Lestage 2003; Higgins et al 2004; Lynch 2004; Mehlman 2004; Newhouse et al 2004). Collected pharmacological data have nevertheless greatly improved our knowledge of fundamental neurobiology and thus have provided supplementary proof in favor of the biological basis of cognitive mechanisms. ACh and DA remain for the time being the two most illustrative examples of the therapeutic approach (Muir 1997; Previc 1999; Southwick et al 2002; Higgins et al 2004) even though peptides, insulin, melatonin or estrogens offer new perspectives (Delagrè and Guardiola-Lemaître 1997; Craft et al 1999; Dubal et al 1999). Steroid hormones clearly modify CNS function as demonstrated by the analysis of the neuropsychiatric correlations observed during the perimenopause period (Feld et al 2005). Cholesterol has recently been at the forefront line of potential cognition-modifiers, any modification of its metabolism, for instance by the statins, having an impact on membrane integrity and intra-neuronal signaling and hence cognitive performance (Xiong

et al 2005). In addition, proteins (β -amyloid and tau proteins) are involved in the memory deficit of AD leading to complex changes in our vision of the biological mechanisms of memory (SantaCruz et al 2005; Lesné et al 2006) and further lengthening the list of compounds implicated in the machinery of memory (Miyashita 2004). When considering the neurobiological targets which, in the near future, could be accessible for drugs (Vakalopoulos 2006; Nichols and Newsome 1999), glutamate and its different receptors, notably NMDA, AMPA or metabotropic glutamate 5 (mGluR5) receptors, appear as excellent candidates (Robbins and Murphy 2006) more precisely in the domain of learning and retrieval (Riedel et al 2003); the role of glutamate in cytotoxicity amplifies the interest of the pharmacology of this system in the neurodegenerative diseases where cognitive impairment is at the forefront.

Neurogenetics

Although at the present time out of the scope of human therapeutics, the genetic basis of cognition and of general cognitive ability appears to be a fascinating approach (Flint 1999; Plomin 1999) for the teams involved in drug discovery. Different genes have been pointed out in different situations from AD (presenilins, apolipoprotein E), dyslexia (chromosome 6) to schizophrenia associated with a pronounced learning deficit (Sanderson et al 1999). Williams syndrome, which is a rare neurogenetic developmental disorder, is a paradigm linking a profound cognitive impairment to a deletion on chromosome band 7q11.23 (Bellugi et al 1999; Levitin 2005). According to Payton (2006) potential pharmacological advantages may be procured from the study of cognitive genetics.

Obstacles facing cognitive pharmacology

Despite the high prevalence of cognitive disorders and the disastrous consequences in terms of individual independence and social and familial relations, health authorities in almost all countries of the world have failed to officially recognize the beneficial effects of cognitive drug therapy outside the realm of symptomatic treatment for AD. Thus, from a regulatory point of view, cognitive pharmacology is limited to three cholinesterase inhibitors (donepezil, rivastigmine, galantamine) and one modulator of glutamate transmission (memantine) (Allain and Bentué-Ferrer 2003). Cognitive and concentration-attention disorders thus remain orphan symptoms even when they occur as part of an identified

condition (parkinsonism, non-AD dementia, depression, post-traumatic stress disorder, schizophrenia) or are the sole expression of an identified cerebral dysfunction (post-ischemia sequela, head trauma, neurogenetic disease).

One of the explanations probably lies in the methodological difficulties inherent in the development of “pro-cognitive” drugs, the main problems including: 1) transposition of a subjective complaint into an objective measurement of performance; 2) the apparent benign nature of the disorder considering the age of the individual; 3) changing classification systems and nosographic considerations (for example, the concept of Age Associated Memory Impairment (AAMI) has changed greatly over the last fifteen years evolving into Age Related Cognitive Disorder (ARCD) then later Mild Cognitive Impairment (MCI), even more recently questioned by Fernandez et al (2005); 4) inadequate and insufficiently sensitive measurement tools for studying cognitive function; 5) the excessively global or composite nature of commonly used evaluation scales; 6) limited therapeutic effects which, moreover, could fade out with time; 7) current debate opposing etiological and symptomatic treatments. In addition to these problems, there is the question, perhaps more psychological than regulatory, of priorities. For example, when associated with another disease, cognitive impairment is often considered a secondary therapeutic objective (memory impairment in Parkinson’s disease or fatigue in multiple sclerosis). Inversely, the risk of deleterious effects on cognition may become the unique consideration when examining certain drugs or drug classes. The example of psychotropics, particularly benzodiazepines, is particularly illustrative since this class of drugs has been associated with memory impairment. The same type of thinking leads to the idea that use of a given compound should be restricted to a given disease and not for pathological conditions occurring within different diseases (cholinesterase inhibitors for example have proven efficacy for cognitive disorders in several diseases such as AD or PD or even attention disorders in children). This type of discordance between regulatory guidelines and proven efficacy necessarily leads to prescriptions outside officially approved indications.

Faced with this dominant attitude of international regulatory authorities, the pharmaceutical industry appears to be gradually slipping away from the objective of developing products which could provide purely symptomatic improvement for the different components of cognition. The fear is that such symptomatic drugs could be sidetracked from their intended use, as has been observed with psychostimulants (ie, amphetamines), producing a negative impact on the drug

development project. This fear is widespread and further exacerbated by the fact that many members of this heterogeneous group of pharmacotherapeutic agents (“cognitive stimulants”, neuron metabolism activators, nootropics) are no longer reimbursed by the French health care fund or have simply been struck off the pharmacopoeia (Mehlman 2004). The current orientation in the pharmaceutical industry is to direct research towards products with more pathophysiological actions, contributing to progress in the concepts of neurocytoprotection and neuroregeneration, at least within the framework of the main neurodegenerative diseases such as AD (Akwa et al 2005) or PD.

In spite of the long-term efforts and initiative of the Nationale Institute of Health (NIH) in the USA to develop cognitive pharmacology (Cutler et al 1985), the National Institute for Health and Clinical Excellence (NICE) in UK, recently reappraised the cost-effectiveness ratio of anti-dementia drugs in a rather critical, controversial and negative way; the debate again cast some shadow over this category of compounds.

Studies in healthy volunteers

A compound’s impact on human cognition is determined from laboratory tests. The procedure is well controlled and standardized: specific test batteries (Table 2) performed by the same subject, according to cross-over designs, clearly lead to the assessment of the compound’s effect on the different components of cognitive functions. Several test batteries are available and commonly used in clinical pharmacology; the comparative advantages or caveats of those procedures are beyond the scope of the review; the question will be either to cover the main cognitive functions performances (Table 2) or rather to deeply analyze the different components of a specific function, such as the different types of memory. Tests are comparative using different doses, with the initial objective of determining the relative safety of the compound under study. It is important to recall that such work, which establishes the “cognitive map” of a given drug, with a detailed description of its effects on given “intellectual” functions, is conducted with healthy volunteers.

Beyond this standard approach, the current objectives of laboratory studies have been broadened to try to demonstrate the real beneficial effect of drugs on cognition. This is a new approach to clinical pharmacology with the goal of developing new treatments for a wide range of indications accompanied by cognitive disturbances: pathological brain aging, dementia (neurodegenerative disease, vascular or HIV-related

Table 2 Measures of performance in clinical pharmacology

A – Psychomotor performance	Actual car driving Simulated car driving Simulated car tracking
B – Sensorimotor coordination speed	Adaptive tracking Critical tracking Continuous tracking Visuo-motor coordination Choice reaction time Simple reaction time Reaction time Pursuit rotor
C – CNS arousal, information processing	Critical flicker fusion Digit symbol substitution task Mental arithmetic Letter cancellation Stroop color test Logical reasoning Visual search task
D – Memory	Short-term memory Continuous memory task
E – Sensory skills	Vigilance task Attention task Continuous attention task Dynamic visual acuity Simulated assembly-like task
F – Motor ability	Finger tapping
G – Physiology	Electroencephalography (EEG) Continuous EEG Multiple sleep latency test Evoked potentials Actigraphy
H – Subjective ratings	Visual analogue rating scales Profile of moods scale Stanford sleepiness scale

Note: From Hindmarch and Shamsi (1999).

dementia), the major psychiatric syndromes and the consequences of head trauma.

In order to ascertain the specific effects of a given drug (psychotropics, psychostimulants, anti-hypertensives, anti-histaminics) on brain processes, early phase trials must comply with standard controlled and validated methodologies. Trials must be conducted in certified laboratories using double-blind experimental protocols versus placebo and a reference product (substances with well-known effects: caffeine, benzodiazepine, amphetamine, clonidine), in young or older healthy volunteers (for certain tasks, it may be useful

to have volunteers with a diminished baseline performance in order to facilitate demonstration of the pharmacological activity and avoid the floor or ceiling effects). The different evaluation criteria require experienced observers to produce valid information. Results must be interpreted with due precautions. Measurements of a given parameter, for example, depend on the degree of motivation or on changes in strategy as well as test-induced fatigue. For each compound evaluated, the risk-benefit ratio can be expressed by the formula I/NI , where I is the number of tests with a significant change in performance score and NI the number of tests with result

scores not different from placebo (Hindmarch and Shamsi 1999). When pharmacokinetic studies are associated, it is possible to link the psychomotor or cognitive effect mathematically to usual kinetic parameters (search for optimal dose and pharmacokinetic-pharmacodynamic modeling [PK/PD studies]). The results obtained in a small number of healthy volunteers are reliable (the disease effect is absent as are cotherapies usually observed in patients) and can be extrapolated to patients in a therapeutic situation; here the exercise will consist in comparing those laboratory studies with the results obtained, with the same drugs, either in the large scale phase III studies or in Pharmacovigilance surveys. The cognitive map thus obtained enables a surmise of more overall and behavioral effects, in patients. For clinical research, ligands specific for certain CNS receptors enable assigning a specific (or selective) role to certain receptors or neurotransmission circuits during a specific phase of data processing in the CNS. As mentioned above, this enables linking data collected from animal models to those observed in human volunteers. The example of the dopaminergic systems is instructive here, since relatively specific agonist and antagonist agents are identified for each of the five subtypes of receptors. In their work with quinpirole, a specific dopaminergic D₂ agonist, Arnsten et al (1995) demonstrated in the monkey that these receptors are implicated in higher cognitive functions such as memory tasks with delayed recall. This observation demonstrated in particular the importance of dosage. Small doses produced a deleterious effect by action on presynaptic autoreceptors altering the animals' performance while high doses on the contrary stimulated postsynaptic receptors improving the same paradigms. It was also instructive to use older monkeys which demonstrated an age-related alteration in the dopaminergic systems with a prefrontal projection and also explained that the deleterious effect of small doses was attenuated or absent, demonstrating probably altered presynaptic structures in these older animals. Other experimental work supported the hypothesis of a role of DA in the function of the prefrontal cerebral cortex (cortical D₁ receptors for example determining the performance on a working memory task) (Nieoullon 2002). Similar results were obtained in healthy volunteers. Servan-Schreiber et al (1998a, b) provided an elegant demonstration that administration of *d*-amphetamine (0.25 mg/kg per os) improves information processing in the brain via dopaminergic transmission, and that the accuracy of complex tasks are improved (probably through improved attention mechanisms) without modifying vigilance. Similarly, recent work by Volkow et al (2000) in

healthy volunteers demonstrated a correlation between age-related dopaminergic activity and performance on different neuropsychological tests. These results provide supplementary proof of the role of the dopaminergic system in cognitive disorders in the elderly subject. Curiously, few studies have been published on available dopaminergic agonists other than piribedil, a D₁, D₂, and D₃ agonist (Schück et al 2002) and apomorphine, a D₁ and D₂ agonist (Luthringer et al 1999; Manfredi et al 1998). These data demonstrate a pro-cognitive and awakening effect of these dopamine agonists (increased beta activity on the EEG, improved delayed recall). These results opened an interesting discussion concerning the attribution of narcolepsy attacks in traffic accident victims (Frucht et al 1999) to ropinirole (D₂ agonist similar to quinpirole mentioned above) and pramipexole (D₂, D₃, D₄ agonist). Several pharmacological classes have been analyzed using the cognitive mapping method mentioned above. This should contribute to better definition of their risk-benefit ratio and their potential indications: nicotine, caffeine, antihistaminics, hypnotics, anxiolytics, antipsychotics (Allain et al 2000a; Gandon and Allain 2002; Patat et al 1996; Patat 2000; Stip et al 1999). In all likelihood, the list of the drugs to be tested according to such a procedure will continue to lengthen for three reasons: 1) sudden increase in the number of drugs available in neurology, 2) overt policy to treat several orphan conditions of the CNS (most of which are dominated by cognitive disorders), 3) worries about drug safety for cognition (Cognitive Pharmacovigilance).

Drugs and memory

Drugs for Alzheimer's disease

Several cholinesterase inhibitors (donepezil, rivastigmine, galantamine) and one glutamatergic neurotransmission modulator (memantine) are officially recognized as beneficial for patients with AD. These compounds were awarded marketing approval on the basis of improved scores on global scales measuring overall cognitive decline and its impact on daily living, and not because of a positive effect on specific memory tests (Lane et al 2006). Such targeted tests would have to exhibit a clear effect before these drugs could be used for MCI (at least for amnesic-MCI, as still controversially considered to be an isolated memory disorder probably announcing AD). Recent studies of cholinesterase inhibitors in MCI have been unable to demonstrate any beneficial effects in terms of symptomatic improvement on memory tests (Allain et al 2004), nor any preventive effect on

conversion to AD (Petersen et al 2005). These negative results, although partially explainable (for instance upregulation of cholinergic systems at the early phase of the disease) continue to discredit the cholinesterase inhibitor class of drugs (Kaduszkiewicz et al 2005).

Antioxidants

At very high doses, vitamin E (tocopherol) does not have any direct effect on memory but it appears to retard by a few months progression to AD and might be helpful for the prevention of other forms of dementia in healthy subjects. Similar results have been obtained with selegiline, a MAO-B (monoamine oxidase type B) inhibitor whose impact on DA concentrations could also have a symptomatic effect by stimulating dopaminergic tone.

Antioxidants, which counteract the deleterious effect of free radicals, cannot be considered as pro-memory drugs per se. They have however opened new avenues of very active research in the field of neuroprotective agents, reflecting the fragile nature of human memory and its vulnerability to aggression (age, depression, anxiety, ischemia-hypoxia, addiction, HIV-related dementia).

Anti-aging drugs

In many countries, a variety of medications are marketed and prescribed for age-related cognitive decline. These old drugs (vasodilators, brain oxygenators, nootropics, cognitive enhancers) (Riedel and Jolles 1996) have been used for years without either formal proof of efficacy in dementia or showing a small effect-size. Aging being a normal physiological process, there is no clear indication for their use. These drugs do however have pharmacological properties quite in line with the multifactorial disseminated nature of memory disorders: membrane fluidification, activation of neuronal energy metabolism, arousal. A few old studies highlight a facilitating effect on memory which might be worth evaluating with modern methodology.

Estrogens

There is a growing body of evidence supporting the notion that estrogens have an impact on memory processes in women (Bentué-Ferrer et al 1999). Much work has demonstrated that menopausal women taking synthetic estrogens in hormone substitutive therapy exhibit better results on memory tests than those not on replacement therapy (Matthews et al 1999; Steffens et al 1999). Conversely, the recent Women's Health Initiative Memory Study which included 4532 menopausal

women aged 65 years or more, found that long-term hormone replacement therapy with synthetic steroid hormones, estrogen and progesterone, increased the risk of probable dementia and did not prevent MCI (Shumaker et al 2003). The debate remains open regarding the beneficial effect of natural or synthetic oestrogens, respectively, on memory in menopausal women (Henderson et al 2003; Sherwin 2005).

Natural substances

A short list of natural substances with a recognized effect on memory performance is presented in Table 3. These compounds, often found in foodstuffs (caffeine, glucose, nicotine), cannot be proposed without the necessary precautions but can greatly contribute to targeted research on the possible impact of future promnestic drugs. This opens new perspectives for a more mechanistic approach to the cellular signaling pathways of memory, for example with the use of phosphodiesterase IV inhibitors increasing CREB phosphorylation (Nagakura et al 2002; Tully et al 2003). New drugs obtained from plant extracts have also received marketing approval, for example *Paullinia cupana* (Kennedy et al 2004) or more recently huperzine, extracted from a lycopod species growing in China (*Lycopodium serratum*) and galantamine, extracted from snowdrop (*Galanthus nivalis*), both indicated for AD (Zangara 2003; Brodaty et al 2005).

Over-the-counter drugs promoted as memory aids cannot be ignored. These drugs most of the time are used as automedication and should be more extensively studied either to clearly demonstrate a significant clinical benefit or to establish their safety profile.

Drug safety and memory

When looking at the pharmacovigilance data, it is important to take into account the sources of information as well as the study conditions and the manner the drug is used. For example, in the treatment of anxiety, benzodiazepines (enhancers of GABAergic neurotransmission), can greatly alter recall after an acute administration, whereas following a chronic treatment, no memory impairment seems to occur, due to a tolerance phenomena (Curran 1991, 1992). This point raises a supplementary problem since most psychiatric diseases (depression, anxiety and schizophrenia) are associated with cognitive disorders often affecting memory, even before any treatment. Psychotropics alleviate many of these disorders. But could their final effects, by possible analogy with work on beta-blockers used for the treatment of posttraumatic stress disorder (Giles 2005; Van Stegeren et al 2002), result from their

Table 3 Natural substances for memory performance

Compound	Proven effects on memory	Comments	Reference
Glucose	+	Acetylcholine synthesis Neuronal metabolism Cerebral plasticity	Hoyer 2003
Nicotine	+	Effects similar to donepezil for piloting performance Indirect effects on glutamatergic, GABAergic, dopaminergic, nicotinic (α_6 , α_7 , $\alpha_4\beta_2$ and β_3) receptors Desensitization of nicotinic receptors	Picciotto 2003 Mumenthaler et al 2003
Caffeine	+	Antagonist of adenosine (A_1) receptors facilitating memory and arousal Role in cerebral neurotransmission homeostasis	Ribeiro et al 2002
Plant extracts: ginkgo, echinacea, kava	+	Used in traditional medicine, they might treat memory disorders	Ernst 2002 Howes et al 2003

amnesic action, helping the patient “forget” distressing memories? It is also important to recall that all compounds with anti-cholinergic effects (tricyclic antidepressants, urological drugs) perturb memory function, mimicking the scopolamine effect used for inducing experimental amnesia (Mintzer and Griffiths 2003; Parra 2003). The impact of these different agents on cognition and memory has to be re-evaluated in the early phases of the disease, in the light of new advances in neuropsychopharmacology. Schematically, new compounds designed for long-term treatments (Z compounds: zopiclone, zolpidem, zaleplon) (Terzano et al 2003; Allain et al 2005), serotonin reuptake inhibitors, antipsychotics (Brunnauer et al 2004) or anticonvulsants do not alter cognition or memory when prescribed at therapeutic doses. Though deleterious effects on memory per se are sometimes difficult to distinguish from other cognitive disorders or from negative impact on vigilance of numerous common drugs (antihistaminics, beta-blockers, illicit drugs including cannabis and 3, 4-methylenedioxymethamphetamine [ecstasy]); drug registries of substances-induced memory impairment provide a rich source of information (Patat 2000; Dafters et al 2004).

Drugs and language

Historical background

The idea that drugs can be used to correct for altered language capacity is not new. As early as 1947, Linn (1947) tested sodium amytal in a woman with ischemic aphasia,

hypothesizing a reduction in the “frustration and inhibition of communication” characteristic of aphasia. Unfortunately, the effect could not be confirmed in a group of 27 patients treated by Bergman and Green (1951) in 1951. Although these early studies did initiate a new domain that could be named “pharmacolinguistics”, with the development of the first psychotropic drugs in the 1960s and 1970s (meprobamate, chlordiazepoxide, methylphenidate) generally, little real progress was made. Since most cases of aphasia occur secondary to stroke, the main objective of subsequent studies was focused on stroke-related mechanisms, with little work directly devoted to language disorders themselves. Even in a most recent review by Shisler et al (2000), and despite the provocative title of “Pharmacological approaches to the treatment and prevention of aphasia”, the discussion was limited to drugs affecting the brain ischemic processes (glutamate modulators, protein kinase C inhibitors, monoganglioside, calcium channel inhibitors, free radical scavengers, and thrombolytic drugs). Not surprisingly, most of the highly interesting work on language disorders (or degenerative diseases like semantic dementia) and drugs has been reported by rehabilitation specialists (Musso et al 1999).

Brain oxygenation

The effect of hyperbaric oxygen therapy has been widely studied, and certain reports have used evaluation criteria clearly belonging to the domain of language (Sarno 1969; Sarno et al 1972) including the Functional Communication

Profile, the Token Test or subsets of the Wechsler Adult Intelligence Scale (WAIS). But it was rapidly recognized that this approach was devoid of any therapeutic benefit. During this period, different groups of drugs, called vasodilators or brain oxygenators, were tested, with the mechanistic hypothesis that they might help restore function in ischemic brain areas. In 1951, Smith and Turton (1951) described very clear improvement in verbal fluency, elocution and “loquacity” in a patient given 40 mg tolazoline after development of an aphasia secondary to stroke. Piracetam, a nootropic agonist of GABAergic transmission also improving oxygen brain bioavailability, given at the dose of 4.8 g/d, has also been found to significantly improve language function in several studies with acceptable methodologies (Huber et al 1997). Other brain oxygenators, such as vincamine or almitrine-raubasine (Enderby et al 1994) can improve elocution and quality of language in “vascular” patients (stroke, dementia) although the linguistic items used for evaluation lacked precision and were buried among other elements in composite evaluation scales. The recent identification of neuroglobulin, a protein that transports oxygen from the blood stream to neurons much like myoglobin in muscles, has recently given new impetus to the oxygen theory (Burmester et al 2000) and to the compounds able to improve brain oxygen availability; apparently this approach did not lead to any real progress in the field of pharmacolinguistics.

Catecholamines

Amphetamine, a noradrenergic and dopaminergic stimulant, has been studied in Broca’s aphasia in a *princeps* case reported by Walker-Batson et al (1990). The positive effect obtained in this unique patient persisted for 12 months and led to further studies that provided less convincing results, particularly since amphetamine was associated with classical language rehabilitation therapy and the studies were not double-blinded (Hassid 1995; Walker-Batson et al 1995).

Likewise bromocriptine, a direct dopamine agonist, has been widely studied. In one case described by Albert et al (1988), objective improvement in the Boston Diagnostic Aphasia Examination persisted for one month even though conversational fluency did not appear to be modified. Unfortunately, except for the studies by Gupta and Mlcoch (1992) who used 10 and 30 mg/day, and by Sabe et al (1992) who used 15 and 60 mg/day, the different reports to date, which have used methodologies of more or less satisfactory quality, have been unable to provide objective evidence of any gain in linguistic performance in a variety of aphasic

patients (Sabe et al 1995). This work has nevertheless rightfully raised the question of the role of DA and the subcortical structures in cognition and language (Cohen and Kegl 1999; Crosson 1999). To our knowledge, the new more specific dopaminergic agonists have not been studied in the “indication” of aphasia, although their impact on language, and even their beneficial effect on other cognitive functions, has been demonstrated.

Cholinergic drugs

According to Small (1994), drugs targeting cholinergic systems have demonstrated a disappointing effect on language and language disorders. Use of cholinesterase inhibitors in the treatment of AD has triggered new debate, but the “aphasia” element remains again just one of the symptoms observed in this degenerative disease, in addition to inaugural and predominant memory disorders. Jacobs et al (1996) have described the beneficial effect of increased brain concentrations of ACh on anomia, correlatively with Tanaka et al (1997) who worked with aphasia patients. The recent case reported by Hughes et al (2000) where adynamic aphasia was related to a subcortical (thalamus-internal capsule) lacuna is instructive: first of all, donepezil, a cholinesterase inhibitor, clearly improved linguistic performance (verbal fluency), and secondly, the benefit persisted beyond treatment withdrawal, raising the question of the role of brain neuroplasticity (Allain et al 1997; Neville and Bavelier 1998) and its cholinergic dependence in language recovery. It is quite difficult to determine the effect of cholinesterase inhibitors (tacrine, donepezil, rivastigmine, galantamine) (Bentué-Ferrer et al 2001) on language and linguistics among the results of phase III trials in dementia that contributed to their marketing approval. Regulatory guidelines were very strict (Allain et al 1998) and the “cognitive” scales (ADAS-Cog, MMS, CGI, GDS) used for assessment contained few linguistic items, despite the frequency and importance of disorders of language comprehension and expression in patients with AD (Grossman et al 1996; Grossman et al 1998).

The effect of ACh (cholinergic agonists and pro-cholinergic drugs) on language may be direct or indirect, but involves two types of central receptors, muscarinic and nicotinic receptors, that beyond language mediate essential cognitive functions in the human brain (Levin and Simon 1998; Jones et al 1999; Paterson and Nordberg 2000; Picciotto et al 2000; Picciotto 2003). In the same line of thinking, few data are available on tolerance of drugs potentially deleterious for language and linguistics.

As a whole, at the present time, no recognized drug can be clearly recommended as an activator or corrector of language in human disease.

Drugs and attention

Attention, as opposed to distraction, involves a sorting process in the planning of a response and thus controls executive functions. Attention processes extract pertinent signals from background noise. They must be distinguished from processes underlying vigilance (arousal) and to a lesser degree working memory. Attention disorders are the correlate of several neuropsychiatric diseases (Berger and Posner 2000) and are in the forefront in AD (Calderon et al 2001), generalized anxiety disease (GAD), schizophrenia, and in attention-deficit-hyperactivity disorder (ADHD) (Elia et al 1999). Attention disorders, irrespective of the severity, have an impact on other cognitive functions (memory and learning, for example) and most importantly potentially perturb execution of daily activities and skills. As emphasized above, anatomical correlates of these processes are known (Fernandez-Duque and Posner 2001; Filley 2002; Raz 2004; Shipp 2004). The psychological mechanisms underlying this function have been described and studied in detail (Awh and Jonides 2001; Cowan et al 2005; Hester and Garavan 2005) enabling the development of tests and procedures for analyzing attention performance in humans (Driver and Frackowiak 2001; Oberauer 2002; Oades et al 2005). These methods are used in clinical pharmacology (Stroop test, continuous performance test, critical tracking task). The neurochemical basis of these functions, mainly neurotransmitters, has also been deciphered so that ACh, amines and glutamate have become selective targets for drugs designed to improve attention and concentration (Coull 1998; Posner and Driver 1992). Paradoxically, the pharmacology of attention disorders has not been developed extensively (Allain et al 2000b) outside the field of ADHD in children where three psychostimulants with aminergic action (amphetamine, atomoxetine, methylphenidate) have been officially recognized as effective (Elia et al 1999; Leonard et al 2004). Neurochemistry has led to numerous publications in animal models (mainly with rodents) which, using specific ligands, demonstrate the action of dopaminergic D₁ (Nieoullon 2002), adrenergic α_2 (Franowicz et al 2002), and cholinergic nicotinic (nAChR) (Levin and Simon 1998; Hahn et al 2003) receptors, all involved in attention/concentration performance. These receptors could legitimately become priority targets for “pro-attention” drugs in humans. This has been corroborated in clinical pharmacology with drugs used for other indications: guanfacine, a central antihypertensive agent and agonist of adrenoceptors α_{2A} (Jakala et al 1999), bupropion, an

inhibitor of DA and noradrenaline reuptake indicated for smoking cessation (Wilens et al 2005), piribedil and pramipexole, antiparkinson D₂ and D₃ agonists (Schück et al 2002; Peretti et al 2004). The most widely studied compounds at the present time are nAChR agonists such as ABT-418 and ABT-089 (Prendergast et al 1998); due to the large number of nAChR subtypes in the CNS, a specific function and the capacity of inducing tolerance or not have to be determined for each ligand. Most likely, cholinesterase inhibitors principally act on attention/concentration by reinforcing the cholinergic tone on the nAChR. Data from humans are however greatly dominated by the search for a deleterious effect on attention, both for psychotropics and illicit drugs (Allain et al 2000a; Patat 2000).

More generally, and beyond the notion of ADHD, attention disorders could be improved by effective drugs currently in the authorization process and awaiting pertinent clinical trials. Broader indications could be outlined, beyond military applications or situations where sustained attention is of prime importance (competition sports, civil aviation, surgery, computer work).

Perspectives–conclusion

The data from literature described here on memory, language, and attention/concentration show that it is too early to try to codify pharmacological strategies for the impairment of these cognitive functions in adult human beings. Despite the recent emergence of cognitive neurosciences (Friederici and Ungerleider 2005) and the development of specific evaluation tools for the different components of cognition in humans, cognitive pharmacology remains in the exploratory phase, with neurobiological concepts that still need to be validated. The fact that cognitive function is never proposed as a major evaluation criterion for large-scale studies or epidemiology clearly illustrates this situation. The data which are available come from pharmacovigilance studies, enabling an evidence-based choice between drugs of a given class (ie, psychotropics) as a function of observed deleterious effects on different components of cognition (for example anxiolytics and antipsychotics for the treatment of agitation in the demented subject). The only drugs with evidence-based indications are used in AD, mainly cholinesterase inhibitors, because of their proven beneficial impact on working memory and attention. Extension of their indications to cognitive disorders associated with vascular dementia (Allain et al 2003), PD (Emre et al 2004), or Lewy body dementia is legitimate. Theoretically, cognitive stimulants and nootropics which have a more global action on neuronal metabolism,

membrane fluidity, and the rate of information processing could be used for a variety of conditions involving altered cognition or attention. Unfortunately, the large number of trials conducted with these compounds has been unsuccessful in convincing the public health authorities. While waiting for products with proven etiopathogenic efficacy (Akwa et al 2005), an alternative therapeutic strategy would be to promote specific symptom relief in a complex disease such as AD, schizophrenia or Huntington's diseases.

To meet the challenges of further development of cognitive pharmacology, there are three requisites: 1) promote large-scale clinical trials centered on cognition in a variety of nosographic entities (Huntington's disease, posttraumatic stress disorder, psychoses, head trauma, stroke); 2) encourage new explorations in neurobiology and proteomics; 3) broaden the scope of pharmacological improvement of cognitive and intellectual functions (eg, choice, decision, perception of time [Vanneste and Pouthas 1999]). This pharmacological and therapeutic approach should enable improvement for a large number of adults suffering socially and professionally from cognitive impairment.

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