REVIEW

Pharmacological aspects of cognitive impairment: past, present and future of drugs in dementia

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Summary

Cognitive impairment is a dramatically increasing problem affecting many individuals as well as the health system. As we have no causal treatment for the loss of memory, symptomatic treatment is needed. Influencing the ACh system is a generally accepted approach, although other therapeutic treatments are in various stages of development. The multiple target drug approach using hybrid compounds may be another optimized move forward for the treatment of cognitive disorders. Since the complex neuronal regulation is slowly being decoded, there is hope that ways will be found to stop neuronal loss and to generate new synapses.

Keywords: cholin esterase inhibitors – NMDA – receptor antagonist – histaminergic neurotransmission – β -amyloid peptide – τ -protein – therapy – animal models – H_3 receptor – histamine H_3

INTRODUCTION

Dementia is a progressive decline in memory and cognitive functions including judgment, decision-making, orientation to physical surroundings, and language. Many diseases are able to cause a

dementia syndrome, but Alzheimer's disease (AD) and cerebrovascular ischemia (vascular dementia) are the two most common. Some cases of dementia involve both of these disorders. The prevalence of dementia is rapidly rising as the percentage of older people in the population increases. It has been estimated that about 5% of adults over 65 years are affected by AD (Bullock 2004). Roughly speaking, age constitutes the main risk factor for dementia. In view of our ageing society, both the number of dementia patients and the economic and social impacts of dementia are expected to grow dramatically. It is forecast that the worldwide number of elderly people suffering from dementia will rise to 63 million in 2030 (65% of those in less-developed regions), and to 114 million in 2050 (74% of those in less-developed regions) (Wimo et

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al. 2003). There is an enormous need to develop both means of earlier clinical diagnosis and novel therapeutic strategies.

Alzheimer's disease is characterized by extracellular neuronal plaques that contain the β -amyloid peptide and intracellular neurofibrillary tangles (NFT), which are composed of hyperphosphorylated forms of the τ (tau)-protein. The condition is accompanied by decreased synaptic density, which may lead to widespread neurodegeneration, loss of synapses, and failure of neurotransmitter pathways. The cognitive deterioration associated with vascular dementia is caused by occlusion of cerebral arteries and loss of cerebral tissue as a consequence of hypertension, diabetes, heart disease, or stroke.

Cholinergic deficits in the brain are invariably found in models of animal cognitive impairment, ageing humans and those with neurodegenerative diseases (Passani and Blandina 2004). Basic and clinical studies have shown that the degeneration of cholinergic basal forebrain neurons innervating the cortex is linked to cognitive decline (Everitt and Robbins 1997, Passani and Blandina 2004). The central function of acetylcholine (ACh) in cognitive processes is generally accepted, though its precise roles remain to be defined. Patients with dementias of various aetiologies have similar decreases in ACh concentration, which implies a similar pathogenesis in the process of cognitive impairment involved in the various disorders (Jia et al. 2004). The central role of this neurotransmitter in cognitive processes does not imply exclusivity, however: a Medline search with the keywords "memory" and various "neurotransmitters" and the limitation for "title words" revealed that essentially all major neurotransmitters have been associated with roles in cognition. An informal (and of course non-representative) "top 10" enumerational list has NMDA in the top spot, followed by dopamine, ACh (3rd rank!), insulin, serotonin, and histamine (special emphasis will be placed on histaminergic neurotransmission later in this paper). According to the same survey, the other catecholamines (epinephrine and norepinephrine) and GABA are in the minor leagues of cognition-supporting endogenous substances. At the end of the list are substance P and the vasoactive intestinal peptide (VIP), with one order of magnitude fewer papers referring to them than the top players.

Malfunction of these neurotransmitter systems may elicit additive or even synergistic effects in conjunction with the cholinergic dysfunction. They are representative of the complex regulation of brain systems affecting cognitive processes (Decker and McGaugh 1991, Givens and Sarter 1997).

The Past

Why does ACh hold a preferential position in our perception? That might have more to do with

opportunity than with true desire: inhibitors of various ACh receptors abound in nature, and plants containing them may derive an evolutionary advantage from their ill effects on the mammals that ingest them. The same either does not apply to other neurotransmitter systems, or if it does, then only to a lesser extent. There is a long history of the love-hate relationships between men (and of course women) and drugs and more generally manipulations of the cholinergic system; essentially every mythology (e.g., Greek, Roman, and Indian) contains similar allusions to magic brews that alter the mind of the recipient.

From a pharmacological perspective, the pinnacle is in the Odyssey, the Homeric description of the encounter of Odysseus (King of Ithaca) with the beautiful sorceress Circe on the island of Aeaea. From a Eurocentric perspective, this story reflects perhaps the best known and the earliest (about 3000 years ago) empirical knowledge of the clinical effects of an anticholinergic substance and the therapeutic efficacy of a cholinesterase-inhibitor antidote (Block 2007).

In brief, when Odysseus and his comrades-in-arms arrived on Aeaea, parts of the crew took a land trip and enjoyed a party given by Circe. At the banquet, they were poisoned with drugs which made them "forget their fatherland and their desire to return to it," and probably also many other things (memory impairment). The sailors also believed they were transformed into animals (delusional-hallucinatory state).

The signs and symptoms described are in line with those induced by the antimuscarinic agents contained in numerous plants: the toxidrome commonly referred to as Central Anticholinergic Syndrome (CAS) (according to Plaitakis and Duvoisin), the drug given to the crew was in all likelihood an atropine-containing extract from *Datura stramonium* (thorn apple, or jimsonweed) (Plaitakis and Duvoisin 1983). Odysseus (with some divine help) set out to save his men. Hermes (at the time in charge of free trade) showed Odysseus the plant containing the needed antidote, which the gods called moly.

The description of the antidote, and the immunity it gave Odysseus, which allowed him to rescue his crew from Circe and to recover their memories, suggest that moly is the acetylcholinesterase inhibitor galantamine, derived from the snowdrop (*Galanthus nivalis* or *Galanthus woronowii*) (Plaitakis and Duvoisin 1983).

As recently as the mid nineteenth century, acetylcholinesterase inhibitors were used on their own to induce mind alterations. Lacking a better judicial system, the natives of Old Calabar, an eastern province of Nigeria, believed in the power of the seeds of a local plant called "chop nut" to determine whether individuals were innocent or guilty. The story of "chop nut" (*Physostigma*

venenosum) and the fundamental Scottish contribution to physostigmine toxicology was recently excellently told by Proudfoot (2006).

Nineteenth-century ophthalmologists were already familiar with the different effects of atropine (mydriasis) and physostigmine (miosis) on the pupil. The knowledge of the mydriatic actions of antimuscarinics is in fact millennia old. Atropine extracts were used by Cleopatra in the last century B.C. to dilate her pupils, in the hope that she would appear more alluring. In the Renaissance, women used the juice of the berries of *Atropa belladonna* (Deadly Nightshade) to enlarge their pupils for the same reason; *bella donna* is Italian for 'beautiful woman'.

The miotic effect of "chop nut" was recognized as soon as sufficient quantities of the plant became available to experiment-friendly European physicians. One of the first to report on physostigmine-induced miosis was Argyll Robertson in 1863 (Proudfoot 2006). With the synthesis of physostigmine (eserine) by P.L. Julian and J. Pikl in 1935, this carbamate derivative, a reversible inhibitor of cholinesterase, became widely available (Julian and Pikl 1935).

At about the same time began the era of irreversible inhibitors of cholinesterase: the organophosphates and organophosphonates. The names associated with the development of these compounds are Willy Lange and his student Gerda von Krueger and Gerhard Schrader in Germany and Bernard C. Saunders in the UK. While these names are known to everyone interested in cholinergic pharmacology, those associated with the first synthesis of an organophosphate cholinesterase inhibitor are little known: De Clermont and Moschnin, two French scientists, synthesized tetraethyl pyrophosphate (TEPP) in 1854, while working in the laboratory of Wurtz (Holmstedt 1963).

It was assumed for a long time that carbamate cholinesterase inhibitors are "natural products" as opposed to organophosphates and organophosphonates, which were considered synthetic or man-made. Recently, however, natural organophosphate cholinesterase inhibitors produced by *Streptomyces antibioticus* have been described (Neumann and Peter 1987).

The Present

The group of clinically available drugs for dementia is rather small: Four cholinesterase inhibitors and a NMDA-receptor antagonist.

Plugging the sink: cholinesterase inhibitors

Tacrine (Cognex[®], Figure 1, (2)): Tacrine is structurally an 1,2,3,4-tetrahydroacridine-10-amine and acts as a reversible inhibitor of both plasma esterase and acetylcholinesterase. It was the first centrally acting cholinesterase inhibitor approved

for the treatment of AD and was marketed under the trade name Cognex. The story of the development of tacrine began in 1940, with its synthesis as an intravenous antiseptic by Adrian Albert at the University of Sydney, Australia. In the 1970s, William Summers began using tacrine in treating drug overdose coma and delirium. He felt it might have application in Alzheimer's treatment based on work done in England by Peter Davies. In 1981, Summers et al. gave intravenous tacrine to Alzheimer's patients, who improved measurably (Summers 2006). Tacrine showed poor bioavailability and a short half-life requiring qid administration. Because of a high incidence of increases in liver transaminases under tacrine therapy (tacrine transaminitis), the substance is *de facto* not used anymore (Green et al. 1995).

Donepezil (Aricept[®], 2-[(1-benzyl-4-piperidyl)methyl]-5,6-dimethoxy-2,3-dihydroinden-1-one) (Figure 2, (2)): Donepezil, a piperidine derivative, is also a reversible inhibitor of acetylcholinesterase, but with a fast onset. It has excellent oral bioavailability and easily crosses the blood-brain barrier. Because of its long half-life, it need only be taken once a day. Donepezil was developed by Sugimoto et al. at the Tsukuba Research Laboratories for Drug Discovery, Eisai Company, Japan (Sugimoto et al. 2002).

Rivastigmine (Exelon[®], (S)-N-ethyl-N-methyl-3-[1-(dimethylamino)ethyl]phenyl carbamate) (Figure 2, (3)): This substance, synthesized by Weinstock et al. at the Hebrew University of Jerusalem, Israel, and developed to market by Novartis, was approved by the FDA for treatment of AD in 2000. While tacrine and donepezil are classified as short-acting or reversible agents, since binding to acetylcholinesterase enzyme (AChE) is hydrolyzed within minutes, rivastigmine is classified as an intermediate-acting or pseudo-irreversible agent because it inhibits AChE for up to several hours. Preclinical biochemical studies indicated that rivastigmine might have some central nervous system selectivity over peripheral inhibition. Further advantages of this carbamate are a metabolism independent of hepatic cytochrome P450 enzymes (pK properties remain essentially unaltered in patients with renal or hepatic impairment) and its availability as a transdermal patch formulation (Jann 2000). In 2006, it became the first product approved globally for the treatment of the dementia associated with Parkinson's disease.

Galantamine (Razadyne[®], (4aS,6R,8aS)-4a,5,9,10,11,12-hexahydro-3-methoxy-11-methyl-6H-benzofuro[3a,3,2-ef][2]benzazepin-6-ol) (Figure 2, (4)): An alkaloid of plant origin, galantamine is a competitive, fast-onset reversible inhibitor of esterases (Lane et al. 2006). It shows a 50-fold selectivity for acetylcholinesterase over plasma cholinesterase (BChE) (Krall et al. 1999).

The compound was FDA-approved for treatment of A) in 2001. Following the deaths of two patients after they were mistakenly given a diabetes medication glimepiride (Amaryl) instead of the Alzheimer's medication galantamine (Reminyl), the manufacturer Ortho-McNeil Neurologics decided to change the latter's name. Effective from July 2005, the Alzheimer's medication changed its name from Reminyl to Razadyne. There have since been reports of another name confusion, between

Razadyne and Rozerem (the trade name for Ramelteon, a medication for the treatment of insomnia, marketed by Takeda) (<http://www.rxforsafety.com/news/index.htm> – accessed on April 19, 2007). Ramelteon is the first in a new class of sleep agents that selectively bind to the melatonin receptors (MT₁ and MT₂) in the suprachiasmatic nucleus (SCN).

Fig. 1. **Tacrine is a potent inhibitor of red blood cell – AChE**, with an IC₅₀ of about 200 nM.

The “better magnesium”

Memantine (Namenda®; Axura®, 3,5-dimethyladamantane-1-amine) (Figure 2, (5)): Glutamate as an agonist at ionotropic excitatory receptors (NMDA) plays an important role in memory function and information processing. It appears that β-amyloid (available in excess as in Alzheimer's disease) inhibits glutamate recycling and leads to glutamate accumulation and therefore

over-excitation and masking of signal transmission (unfavorable noise-to-signal ratio). Memantine restores physiological transmission by blocking NMDA receptors.

As a result of its less pronounced voltage dependency, memantine is more effective than Mg²⁺ in blocking pathological activation of NMDA receptors. However, following strong synaptic activation, memantine, like Mg²⁺, can also leave the

NMDA receptor channel. Compared to the body's own NMDA antagonist magnesium, memantine is described as a "better magnesium" (Rogawski and Wenk 2003, Lipton 2004). In addition to having NMDA effects, memantine is also a potent antagonist at serotonin 5-HT₃ receptors and a weak antagonist at neuronal nicotinic receptors. Memantine has an excellent bioavailability of close to 100% and a long half-life similar to that of donepezil (60–90 hours). Hepatic CYP metabolism is minimal; most of the drug is excreted renally, either unchanged or conjugated. Memantine is generally co-administered with a cholinesterase inhibitor, the pairing with donepezil being advantageous because of its comparable half-life.

The future: nitromemantines

The role of nitrosylation in control of NMDA-receptor functioning is superbly explained by Stuart Lipton, who is the father of the "nitromemantines" (Lipton 2004). In brief, while several cysteine residues on the NMDA receptor can be nitrosylated, cysteine 399 seems to mediate over 90% of the NO effect on the NMDA receptor. Nitrosylation at this site modulates NMDA-receptor functioning, reducing Ca²⁺ influx into the cell and thus reducing excitotoxicity. Nitromemantines are perceived to have great potential as NMDA modulators.

Turning on the ACh tap: stimulation of 5-HT₄ receptors

5-HT₄ receptor agonists have been around for some time and have been employed, with mixed results, in the treatment of gastrointestinal disease. Some of the best-known examples are cisapride (Propulsid®), a gastrokinetic drug, and tegaserod (Zelnorm®), used for the management of irritable bowel syndrome with constipation. More recently, mosapride (Gasmotin®) has been marketed by Daiippon Sumitomo Pharma as a gastrokinetic drug. Marketing of both cisapride and tegaserod has been restricted in the United States because of their torsadogenic potential (potassium channel blockade); however, their main mode of therapeutic action was the release of acetylcholine via activation of the serotonin 5-HT₄ receptor. In addition, 5-HT₄ activity is associated with an increased excretion of a soluble form of the amyloid precursor protein sAPPα (the "good" APP). The insoluble form of this protein (the "bad" APP) deposits in plaques in the brains of Alzheimer's patients. Thus, increasing the good APP is believed to be advantageous. Centrally acting 5-HT₄ receptor agonists are a promising new avenue in Alzheimer's research being pursued by some of the major drug companies.

Fig. 2. Group of clinically available drugs used primarily for treatment of dementia.

Histaminergic neurotransmission

The histaminergic system is strongly associated with numerous activities of arousal, learning and memory, neuroendocrine regulation, vascular function, and processes in the central nervous system (Panula et al. 1997). Since systemically applied histamine does not cross the blood-brain barrier, the central nervous system (CNS) depends upon local neuronal biosynthesis. Morphological features such as compact and widespread distribution of the varicose fibers suggest that the central histaminergic system may act as a main regulatory centre for whole-brain activity and interact with numerous other neurotransmitters (Brown et al. 2001, Wada et al. 1991).

Histamine has been called a “waking amine,” because it has been shown that histaminergic activity increases significantly during awake periods (Monti 1993). The diurnal changes in brain histamine levels indicate a twenty-four hour rhythm (Orr and Quay 1984); for example, the catabolic activity of histamine *N*^ε-methyltransferase (HMT) is higher during darkness (Tuomisto and Tuomisto 1982).

Four distinct histamine receptor subtypes (H_1 – H_4) have been identified, and all are G protein-coupled receptors. They are all found in different

concentrations in the CNS (Ligneau et al. 2000, Cogé et al. 2001). H_3 receptors occur both as autoreceptors on histaminergic nerve endings, controlling synthesis as well as release of histamine by a negative feedback mechanism (Arrang et al. 1987, Prast et al. 1994), and as heteroreceptors, modulating the release of numerous other neurotransmitters (e.g., glutamate, dopamine, ACh, noradrenaline, serotonin, GABA, some peptides and co-transmitters) (Schlicker et al. 1988, 1989, 1993, 1999, Chotard et al. 2002).

In addition to having profound effects on arousal, H_3 receptors have been reported to play a strong role in cognition (Wada et al. 1991, Passani and Blandina 1998). The histaminergic system has a neuromodulatory effect on cholinergic transmission via H_3 receptor-mediated inhibition in different brain areas, rat hippocampus (Bacciottini et al. 2002), cortex (Blandina et al. 1996), ventral striatum (Prast et al. 1997), and basolateral amygdale (Passani et al. 2001). H_3 receptors modulate acetylcholine release differently, depending on the brain region and the neurological status (Passani et al. 2004).

Fig. 3. Structures of potent H_3 receptor antagonists.

Inhibition of cortical acetylcholine release by H_3 receptor activation is indirect and appears to be mediated by GABAergic interneurons in the cortex (Giorgetti et al. 1997, 2000). Endogenous histamine exerts a tonic influence on cholinergic neurotransmission, enhancing cholinergic activity at the level of cholinergic cell bodies in the basal forebrain (Mochizuki et al. 1994, Cecchi et al.

1998, Bacciottini et al. 1999). Selective antagonists and inverse agonists block H_3 autoreceptors and stimulate ACh release.

Along with ACh interactions of H_3 receptors, histamine modulates NMDA receptors (Bekkers 1993). Although this effect is not mediated via histamine receptors, the histamine liberated by H_3 blockade may facilitate long-term potentiation

(Selbach et al. 1997), providing additional support for a central role of histamine in cognition.

H₃ Receptor antagonists in cognition models

Numerous histamine H₃ receptor antagonists have demonstrated procognitive effects in memory consolidation models. In step-through passive avoidance responding, a model relevant to memory consolidation, thioperamide as a classical reference antagonist reversed impairment in memory and learning in a mouse strain with premature senescence (Meguro et al. 1995).

The utility of H₃ receptor antagonists in neurodegenerative disorders is shown in passive avoidance and novel object recognition tests (Giovannini et al. 1999), the Morris water maze, Barnes maze and elevated plus maze models (Hancock and Fox 2004), and models of attention and impulsivity, as well as multiple-choice serial reaction time tasks (Muir et al. 1994, Everitt et al. 1995); H₃ receptor antagonists also attenuate slow-wave electroencephalograph activity. These effects are consistent with increased alertness, vigilance, and attention (Table 2) (Ligneau et al. 1998).

As many early potent histamine H₃ receptor antagonists containing an imidazole moiety showed potential limitations concerning selectivity and especially pharmacokinetic properties (CYP interaction), the development shifted to so-called non-imidazole derivatives, which are currently in various clinical phases (LaBella et al. 1992, Ganellin et al. 1998, Ligneau 2000, Lovenberg et al. 2000, Hough 2001, Ireland-Denny et al. 2001, Liu et al. 2001, Hahn et al. 2002, Yang et al. 2002, Yao et al. 2003, Esbenshade et al. 2003).

Different interesting compounds are shown in Figure 3. The outcome of H₃ receptor antagonist testing in different models of memory, cognition, and related topics has been proved many times (Table 2). The cognitive performance of rat pups was improved in a five-trial avoidance test (attention test) (Esbenshade et al. 2003, Esbenshade et al. 2004, Fox et al. 2005). The social memory effect was also significantly enhanced in the adult rat (Esbenshade et al. 2003, Esbenshade et al. 2004). The social memory test relies on the retention in the memory of olfactory cues, which allow an adult rat to recall a social interaction with a novel juvenile rat for a period of time.

Several potent H₃ antagonists applied orally provided an increase in wakefulness without influencing the locomotor effect. These antagonists have not produced any alteration of the EEG power spectral activity in contrast to amphetamine and therefore preserve the qualitative aspect of vigilance (Leurs et al. 2005, Ligneau et al. 2007). Beside the wakefulness promoting effect both compounds demonstrated in mice or rats, they also showed an antiepileptic effect in dogs, which was comparable to that of desipramine (a tricyclic

antidepressant used to treat human cataplexy) (Bonaventure et al. 2007).

Pharmacological evaluation of different H₃ receptor antagonists proved this class of drugs to be a promising candidate to be developed for the treatment of memory deficits and other cognitive disorders. The compounds increased dopamine and acetylcholine levels in microdialysates of the prefrontal cortex; enhanced fast cortical electroencephalograph rhythms, known to be associated with improved vigilance; and had a marked waking effect. These results, as well as the effect on the two-trial object recognition test in mice (with either scopolamine-induced or natural forgetfulness), underlined the therapeutic potential of these drugs for treating cognitive deficits in AD, other dementias, or attention deficit-hyperactivity disorders (ADHD) (Giovannini et al. 1999, Stark 2004a, Leurs et al. 2005, Bonaventure et al. 2007, Ligneau et al. 2007).

Hybrid compounds – multiple targeting

Combinations of different pharmacological properties in one molecule may produce synergistic effects, i.e., the whole becomes more than the sum of its parts. Dual H₃ receptor and M₂ receptor antagonists have been patented for potential use in AD (Ting et al. 2003). Tacrine has been another chemical starting point of numerous hybrid compounds with dual targeting (Munoz-Torrero and Camps 2006). Here it is of special interest that tacrine is also a potent inhibitor of histamine N^c-methyltransferase (HMT) (Cumming and Vincent 1992, Morisset et al. 1996, Grassmann et al. 2003, Apelt et al. 2005). Inhibition of H₃ autoreceptors would lead to an increased release of histamine due to the inhibition of the negative feedback mechanism. At the same time, competitive inhibition of the catabolic HMT would prevent metabolism of the histamine released. This dual action should lead to a massive and sustained release of histamine within the brain. By combination of antagonist H₃ receptor and inhibitory HMT pharmacophores a new hybrid approach has been realized (Meier et al. 2001) (Figure 3, (9)). For certain compounds (Stark 2004b, Apelt et al. 2005), additional inhibitory activities on AChE and butyrylcholinesterase (BChE) were demonstrated, leading to a quadruple activity profile (Petroianu et al. 2005).

Conclusion

Cognitive impairment is a dramatically increasing problem affecting many individuals as well as the health system. As we have no causal treatment for the loss of memory, symptomatic treatment is needed. Influencing the ACh system is a generally accepted approach, although other therapeutic treatments are in various stages of development (Burns and O'Brien, 2006, Melnikova 2007).

Table 1: **Overview of the clinically available cholinesterase inhibitors** (Krall et al. 1999, Cummings 2000, Delagarza 2003, Lipton 2004, Lane et al. 2006, Lleo et al. 2006).

Substance	Trade name	Chemical structure	Inhibits	t1/2 (min)	Protein binding %	Metabolism	ADR
Tacrine	Cognex 1993	Acridine	reversible; non-competitive BChE>AChE	90-120 min qid	75	Hepatic CYP 1A2 & 2D6	LFT ↑
Donepezil	Aricept 1996	Piperidine	reversible; mixed AChE>>> BChE	70 hours qid	>90	Hepatic CYP 3A4 & 2D6	nausea vomiting
Rivastigmine	Exelon 2000	Carbamate	pseudo-irreversible; non-competitive AChE >BChE	10 hours bid	40	Non-hepatic; Esterases	nausea vomiting
Galantamine	Reminyl Razadyne 2001	Alkaloid	reversible; competitive AChE>BChE	5-9 hours bid	10-20	Hepatic CYP 3A4 & 2D6	nausea vomiting

Table 2: Testing of H₃ receptor antagonists on preclinical animal models of cognition disorders and related topics.

Test model	Relevant Human Disease	Histamine H ₃ receptor antagonists							
		Thioperamide (6) ^{1,2}	Ciproxifan ^{3,4,5}	GT-2331 ^{2,6}	A-304121 ^{2,5}	ABT-239 ^{2,7,8}	JNJ-5207852 ^{9,10}	BF2.649 (7) ¹²	GSK189254 (8) ^{10,11}
Memory Consolidation	AD	+							+
Spatial Orientation	AD	+	+	+		+	+		+
Working Memory	AD	+							
Social Memory	AD	+	+	+	+	+		+	
(Short-term Memory)	ADHD								
Attention/Impulsivity	AD	+	+	+	+	+	+	+	+
Acquisition test in SH rat	ADHD								
5-trail version									
Locomotor activity	ADHD	no change	no change	no change	no change	no change	no change	no change	
Sensory Gating and Pre-attention in mice	ADHD	+	+	+		+	+		
	Schizophrenia								
	AD								
Free moving EGG	ADHD	+	+	+	no change	+	+	+	
Wakefulness state	Schizophrenia								

+ Indicates efficacy in the test model for the specific compound
AD Alzheimer's disease, ADHD Attention-deficit hyperactivity disorder

¹Meguro et al. 1995

²Hancock 2006

³Ligneau et al. 1998

⁴Fox et al.2002

⁵Fox et al. 2003

⁶Tedford et al. 1998

⁷Cowart et al. 2004a

⁸Cowart et al. 2004b

⁹Barbier et al. 2004

¹⁰Bamford et al. 2004

¹¹Medhurst et al. 2007

¹²Ligneau et al. 2007

The multiple target drug approach using hybrid compounds may be another optimized move forward for the treatment of cognitive disorders (Morphy et al. 2004, Roth et al. 2004, Stark 2004a). Since the complex neuronal regulation is slowly being decoded, there is hope that ways will be found to stop neuronal loss and to generate new synapses. This brief overview should be ended with a perspective citation from Corrie ten Boom: "Memories are the key not to the past, but to the future."

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