Ipidacrine and Cholinergic Pharmacotherapy: Are we Getting Closer to the Miracle Drug?

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Abstract

One of the major achievements in the modern era of neurophysiology has been the discovery of acetylcholine as the first ever detected and synthetized neurotransmitter. Soon after, the interest of pharmacology and therapeutics has wide opened the gates of research and cholinergic drugs, along with anticholinesterase principles, have been continuously studied and applied in revolutionary, pioneering experimental work. Famous names such as Henry Dale and Otto Loewi contributed essentially. The spectrum of cholinergic deficiencies with clinical importance has meanwhile been enlarged from central nervous system disorders (dementia above all) to periphery (mainly polyneuropathy and myasthenia). The paper will discuss briefly the history of anticholinesterase drugs since the first findings with the tropical plant of Physostigma venenosum, with actual up-to-date and new formulations (such as rivastigmine, donepezil, ipidacrine) that have enriched substantially in the therapeutic armamentarium of a diversity of medical conditions.

Keywords: cholinergic system; anticholinesterase; tacrine; ipidacrine; dementia; polyneuropathy.

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INTRODUCTION

The history of cholinergic transmission and functioning is indelibly connected with the name of Otto Loewi, Henry Hallett Dale and other enlightened physiologists of the period during the turn of XIX and XX centuries (1, 2, 3). The ‘vagusstoff’ (German term for the vagal agent) was uncovered in a very famous experiment of Loewi: he stimulated the vagus nerve of the heart, collected the perfusate and applied it to a second heart that slowed down exactly as the first one did following the vagal stimulation (4).

It was however, not an unknown issue for the chemistry: Baeyer acetylated choline using acetylchloride in 1867 (5, 6). However, physiological effects of acetylcholine (ACh) were studied some decades later, with the list of cholinergic agonists becoming copious time after time. Taylor grossly separates these drugs in two groups:

a. Acetylcholine and several synthetic choline esters,

b. Naturally occurring cholinomimetic alkaloids (pilocarpine; muscarine) and their synthetic analogues (7).

ACh is a ubiquitous, small molecular weight neurotransmitter which has a fundamental role in chemical neurotransmission in the central (CNS) and peripheral nervous system (PNS) (8). Interestingly enough and maybe without relating findings directly to the mother molecule (i.e. ACh itself), principles able to imitate cholinergic effects were uncovered since the remote years 1840-1850. The alkaloid physostigmine was obtained from Calabar bean (Nigeria), the seed of the perennial plant (Physostigma venenosum) grown in the tropical Africa, in the distant year of 1855 from Sir Robert Christison (9, 10). Once the existence of specific enzymes able to degrade ACh and stop its activity was detected, it was the time for anticholinesterases to take flight. Before finding their deserved place in pharmacies, anticholinesterase drugs were widely used initially as insecticides (parathion, malathion) and as notorious chemical weapons (sarin, tabun and other highly lethal forms). Hence also, the high level of necessary monitoring during the therapeutic use of approved drugs.

Pharmacological history

Effects of cholinergic drugs might have been among the first examined in the modern pharmacology. Pilocarpine, carbachol and ACh act directly at the neuromuscular junction; whereas the anticholinesterase inhibitors (anti-ChE), bind to acetylcholinesterase (AChE) mainly (but not exclusively) at the neuromuscular junction, resulting in a buildup of acetylcholine and stimulation of the parasympathetic nervous system (11).

ACh has been widely considered as acting on the synapse, but its direct effect on the axon conduction are seen as controversial, if not completely absent (12). The first indexed paper on eserine (a synonym to physostigmine) in PubMed dates back in 1878 while showcasing the good effects of the drug in the treatment of the idiopathic mydriasis; while already considered as
efficacious in glaucoma (13). Instead, *physostigmine* as such a term, is mentioned in PubMed initially in 1905, in a paper that scrutinized effects of the latter, of pilocarpine (a genuine cholinergic drug) and atropine over the involuntary muscle, and once again on the paralysed iris (14). The era of anticholinergic drugs – eserine (physostigmine) had just opened the horizons of fruitful research. Chemistry in fact, preceded medicine: Clermont in 1854 already synthetized a potent compound of the anti-ChE series (15).

Gradually other molecules were elaborated: *neostigmine* (prostigmin) has been used in the treatment of myasthenia gravis, acute pseudo-colonic obstruction (Ogilvie syndrome) due to its prokinetic activity, as well as in cases of urinary retention of non-obstructive character. In fact, the drug was introduced into therapeutics in 1931 for its stimulant action on the intestinal tract (16). It has, among other, an impressive number of chemical synonyms whose usage is exchangeable: polstigmine, proserine, prostigmin, synstigmin and syntostigmine (17).

**Modern therapeutics**

Once the AChE inhibitors gained citizenship in field of therapeutics, their number has been continuously increasing. The Table 1 below summarizes some of the preparations included in the Goodman and Gilman’s Pharmacology, with a variety of clinical conditions that might be influenced and eventually treated herewith (15).

<table>
<thead>
<tr>
<th>Table 1. Chemical names of principal anticholinesterase inhibitors</th>
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<tbody>
<tr>
<td>AChE Inhibitors</td>
</tr>
<tr>
<td>Physostigmine</td>
</tr>
<tr>
<td>Neostigmine</td>
</tr>
<tr>
<td>Ambenonium</td>
</tr>
<tr>
<td>Pyridostigmine</td>
</tr>
<tr>
<td>Edrophonium</td>
</tr>
<tr>
<td>Rivastigmine</td>
</tr>
<tr>
<td>Tacrine</td>
</tr>
<tr>
<td>Ipidacrine</td>
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<tr>
<td>Donepezil</td>
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<tr>
<td>Galantamine</td>
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</table>

Albeit it is really difficult to find a highly selective AChE inhibitor that would act only centrally or in the periphery (eventually as a centrally acting acetylcholinesterase inhibitor without effects of the enzyme of the peripheral nervous system; and vice versa), the majority of preparations act centrally. Hence the wide spectrum of their application, such as primarily for dementia in general and memory loss in the narrow sense of the word (Rivastigmine; Ipidacrine; Donepezil; Galantamine). The clinical conditions include Alzheimer’s disease, dementia within the Parkinson disease, autism, Lewy body dementia (18). These diseases obviously imply a cholinergic deficit in the central synapses; when the effects and the deficiency of ACh in the periphery is by far more dramatic, more easily demonstrated and that has been studied since almost two centuries: the case of myasthenia gravis as a disease of the...
neuromuscular junction is illustrative. Paralytic ileus and atony of the urinary bladder are an extension of their efficacy into the smooth muscle activity.

**Tacrine and Ipidacrine**
The principal bulk of studies on *Ipidacrine* comes from Russian and Japanese scholars. However, the mother drug Tacrine, initially marketed under the name of Cognex®, has been actually superseded from recent molecules of a larger efficacy and safety. The chemical molecule *Tacrine* (1, 2, 3, 4-tetrahydro-9-aminoacridine), which was the first ever approved medication against Alzheimer’s disease, was first synthesized by the Australian chemists Adrien Albert and Walter Gledhill at the University of Sydney in 1945 (19). The first mentioning of its pharmacological and therapeutic potency in medical literature came in the early sixties of the last century (20).

**Table 2. Summary of PubMed indexed papers mentioning Ipidacrine (21-43)**

<table>
<thead>
<tr>
<th>CNS diseases / disorders</th>
<th>PNS / autonomous nervous system diseases / disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Authors, year</td>
<td>Diagnose / clinical situation</td>
</tr>
<tr>
<td>Burov et al, 1991</td>
<td>Learning and memory</td>
</tr>
<tr>
<td>Shevtsov et al, 2008</td>
<td>Alzheimer</td>
</tr>
<tr>
<td>Morozova et al, 2008</td>
<td>Neurocognitive deficits / schizophrenia</td>
</tr>
<tr>
<td>Komandenko et al, 1998</td>
<td>Stiff man syndrome</td>
</tr>
<tr>
<td>Kojima et al, 1998</td>
<td>Dementia</td>
</tr>
<tr>
<td>Maksimova et al, 2013</td>
<td>Circulatory encephalopathy</td>
</tr>
<tr>
<td>Maksimova et al, 2013</td>
<td>Ischemic stroke</td>
</tr>
<tr>
<td>Skoromets et al, 2013</td>
<td>Chronic brain ischemia</td>
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As with many other preparations, newly derived formulas superseded the mother drug. Ipidacrine (marketed as Neiromidine® or Neuromidine) was previously known as amiridin and its formula was shortened under the acronym NIK-247. It came into the therapeutic focus as a memory enhancer and thus, a promising anti-dementia drug (21). Table 2 summarizes the principal bulk of studies and diagnoses where the efficacy of Ipidacrine seems tested by far.

Impressive is, of course, not only the highly selective experimental character of some papers during the scrutiny of the effects of ipidacrine (muscarinic receptors; potassium currents; scopolamine-induced amnesia etc.) but also the fact that once the drug was tested for CNS disorders, the attention gradually shifted towards PNS occurrences as well (neuropathies). Among valid up-to-date indications of ipidacrine actually we can include peripheral nervous system diseases (neuritis, polineuritis, polyneuropathy, polyradiculoneuropathy, myasthenia and myasthenic syndrome) as well as disorders of the central nervous system (memory disorders of different origin, Alzheimer's disease and other forms of senile dementia).

**CONCLUSIONS**

Anticholinesterase drugs are an important part of therapeutics in neurology and psychiatry. Experimental paradigms of evaluating the degree of their efficacy and incisive effects have proposed among other, very interesting ways of monitoring: yawning as a sign of parasympathetic central activity, and fasciculations as a sign of this activity in the PNS (44). The omnipresence of acetylcholine and its involvement in basic, important and salient neurotransmission chains, almost in every species, might have been the main cause of such an experimental impetus and success (45).

**REFERENCES**

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