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Review Article

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Multi Target Neuroprotective and Neurorestorative Anti-Parkinson and Anti-Alzheimer Drugs Ladostigil and M30 Derived from Rasagiline

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Present anti-PD and -AD drugs have limited symptomatic activity and devoid of neuroprotective and neurorestorative property that is needed for disease modifying action. The complex pathology of PD and AD led us to develop several multi-target neuroprotective and neurorestorative drugs with several CNS targets with the ability for possible disease modifying activity. Employing the pharmacophore of our anti-parkinson drug rasagiline (Azilect, N-propagrgyl-1-R-aminoindan), we have developed a series of novel multi-functional neuroprotective drugs (A) [TV-3326 (N-propargyl-3R-aminoindan-5yl)-ethyl methylcarbamate)], with both cholinesterase-butyrylesterase and brain selective monoamine-oxidase (MAO) A/B inhibitory activities and (B) the iron chelator-radical scavenging-brain selective monoamine oxidase (MAO) A/B inhibitor and M30 possessing the neuroprotective and neurorescuing propargyl moiety of rasagiline, as potential treatment of AD, DLB and PD with dementia. Another series of multi-target drugs (M30, HLA-20 series) which are brain permeable iron chelators and potent selective brain MAO inhibitors were also developed. These series of drugs have the ability of regulating and processing amyloid precursor protein (APP) since APP and alpha-synuclein are metaloproteins (iron-regulated proteins), with an iron responsive element 5"UTR mRNA similar to transferring and ferritin. Ladostigil inhibits brain acetyl and butyrylcholinesterase in rats after oral doses. After chronic but not acute treatment, it inhibits MAO-A and -B in the brain. Ladostigil acts like an anti-depressant in the forced swim test in rats, indicating a potential for anti-depressant activity. Ladostigil prevents the destruction of nigrostriatal neurons induced by infusion of neurotoxin MPTP in mice. The propargylamine moiety of ladostigil confers neuroprotective activity against cytotoxicity induced by ischemia and peroxynitrite in cultured neuronal cells. The multi-target iron chelator M30 has all the properties of ladostigil and similar neuroprotective activity to ladostigil, but is not a ChE inhibitor. M30 has a neurorestorative activity in post-lesion of nigrostriatal dopamine neurons in MPTP, lacatcystin and 6-hydroxydopamine animal models of PD. The neurorestorative activity is related to the ability of the drug to activate hypoxia inducing factor (HIF) which induces the production of such neurotrophins as brain-derived neurotrophic factor (BDNF), vascular endothelial growth factor (VEGF) and erythropoietin as well as glia-derived neurotrophic factor (GDNF). The unique multiple actions of ladostigil and M30 make the potentially useful drugs for the treatment of dementia with Parkinsonian-like symptoms and depression.

Key words: brain selective MAO inhibition, multi-target drugs, neuroprotective and neurorestorative drugs, antidepressant activity

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IDENTIFICATION OF SELEGILINE AND RASAGILINE AS ANTI-PARKINSON DRUGS

In 1972 Knoll and Magyar [1] described an irreversible monoamine oxidase (MAO) B inhibitor, l-depreny (also now known as selegiline; Fig. 1) derived from l-amphetamine. This drug had failed as an anti-depressant. An important pharmacological property of selegiline was that it did not potentiate the cardiovascular sympathomimetic effect of tyramine, a major side effect associated with the classical first generation of MAO inhibitor anti-depressants. This property of selegiline, together with observation that the basal ganglia of human brain possessed predominantly MAO-B that could metabolize dopamine led us to initiate a pilot study with selegiline in Parkinson's disease [2]. This was followed by two other major studies with drug [3, 4] that led to establishment of selegiline as anti-Parkinson drug and its eventual approval in Europe, USA and worldwide. We had in our possession a series aminoindan propargylamine MAO inhibitors, which were restricted analogue of selegiline. In 1978 we demonstrated that one of these compounds AGN1135 was also a selective irreversible MAO-B inhibitor, which made it the second such drug to be described [5]. The aminoindan ring structure, AGN 1135 results in a mixture of two isomers and the R(+) enantiomer of AGN 1135 was nearly three orders of magnitude more potent than the S(+) enantiomer, TVP1022, in inhibiting MAO-B [5]. Rasagiline (Azilect) is significantly more potent as an MAO B inhibitor *in vivo* as compared with selegiline [6] and has been shown to have anti-Parkinson activity in early and late stages of the disease and approved by FDA [7].

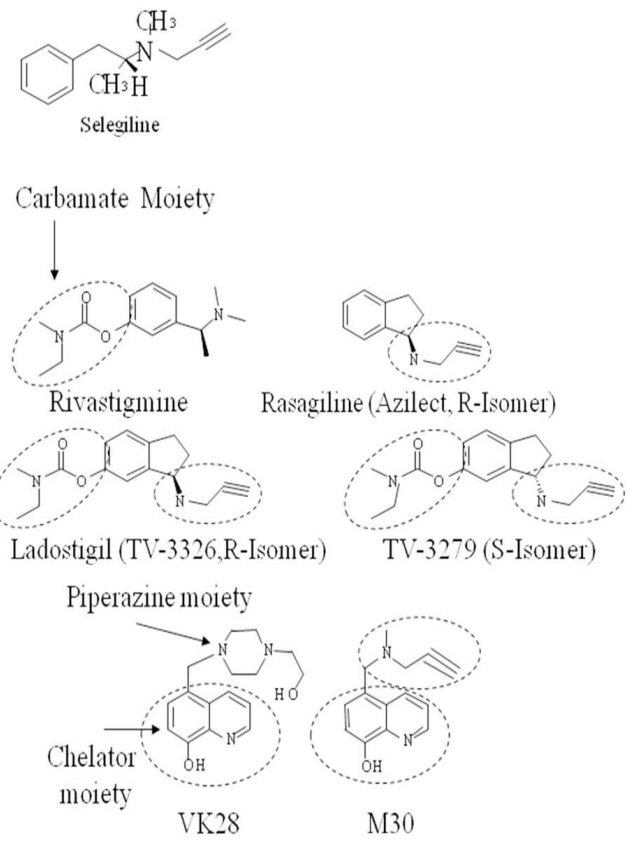

Fig. 1. The structures of propargylaminne possessing selegiline, rasagiline and multi-target drugs ladostigil, M30 and HLA20.

NEUROPROTECTIVE AND NEURORESUE ACTIVITIES OF SELEGILINE AND RASAGILINE

Selegiline has been shown to protect neuronal cells from the consequences of oxidative stress and variety of neurotoxins [8] which could explain its ability to slow the progression of symptoms in PD [9] and possibly in AD [10, 11]. However, the formation of neurotoxic metabolites, amphetamine and methamphetamine may reduce its neuroprotective potential [12, 13]. By contrast, rasagiline does not have neurotoxic metabolites, whose major metabolite, aminoindan has neuroprotective activity in several neuronal cell culture systems and is protective against the neurotoxic effect of amphetamine and methamphetamine [12] and in 6-OHDA mice model [14]. Rasagiline provides neuroprotection against neuronal cell death by preventing the fall in the mitochondrial potential induced by oxidative stress and by increasing the activity of anti-apoptotic factors like BCl2 and antioxidant enzymes [15]. Rasagiline also has neuroprotective effects *in vivo*. It accelerates the recovery of motor function and spatial memory after closed head injury in mice [16] and reduce the incidence of stroke and increases survival in stroke-prone spontaneously hypertensive rats [17]. This protective effect does not only result from MAO-B inhibition, as it is found in other propargylamine-containing molecules that do not inhibit this enzyme, such as the s-optical isomer of rasagiline, TVP1022 and is related to the propargylamine moiety [18]. Both selegiline and rasagiline have neuroprotective activity in the MPTP and lacatcystin models of PD [7]. However, rasagiline has neurorestorative activity in MPTP- and lactacystin-induced degeneration of nigrostriatal dopamine neurons [19, 20]. The molecular mechanism has been shown to be related to the ability of rasagiline to induce PKCα and ε, GDNF and BDNF [7, 14, 19] and is the property of the propargylamine moiety of rasagiline [18].

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MULTI TARGET NEUROPROTECTIVE ANTI ALZHEIMER DRUGS, LADOSTIGIL AND M30, AS A DERIVATIVE OF RASAGILINE

The cardinal features of Alzheimer's disease (AD) are progressive memory deterioration and disordered cognitive function resulting from a loss of cholinergic transmission in cortical brain regions innervated by neurones arising in the nucleus basalis of Meynert [21]. The presence of extracellular plaques containing deposits of proteins and β-amyloid, and intracellular neurofibrillary tangles are hallmarks of the pathology of AD and are thought to contribute to the cognitive deficit. These may result from destructive processes involving the disruption of microtubule assembly and synaptic loss [22]. They could contribute to further neuronal damage and disease progression. In a significant proportion of AD patients there is also a slowing of motor activity and extrapyramidal dysfunction resembling that seen in PD [23, 24]. Furthermore, significant percentage of PD subjects also develops Alzheimer type dementia at late stage of the disease.

The second most common form of dementia is that of the Lewy body type [25], which is characterised by the presence of intracytoplasmic, eosinophilic, neuronal inclusion bodies in the neocortex, limbic areas and subcortical nuclei [26]. These are thought to be responsible for the neuronal damage and give rise to the cognitive deficits, extrapyramidal symptoms and behavioural abnormalities. Depressive symptoms occur in a large proportion of subjects with AD and DLB dementia [27] and with PD [28]. This has been attributed to degeneration of noradrenaline and serotonin neurones innervating the limbic system [29].

Although there is still no definitive consensus on the aetiology of either AD or PD, clear evidence exists for defects in mitochondrial function, dysregulation of brain iron, inflammatory responses and energy metabolism in these conditions. Significant decreases in the oxidative metabolism of glucose are seen in cortical and nigral areas at relatively early stages of AD and PD respectively [30] together with a reduction in the number of glucose transporters [31]. There is evidence of a decrease in the activity of catalase in the parietotemporal cortex and basal ganglia of AD post-mortem brains with no change or an increase in the activity of superoxide dismutase [32] and increase of MAO-B in glial cells [33]. These enzymatic changes could contribute to oxidative stress through the formation of higher levels of hydrogen peroxide. A failure in mitochondrial enzyme activity is indicated by the finding of a reduction of cytochrome oxidase in AD [34] and of NADH dehydrogenase in PD [35]. In each of these conditions, damage from free radicals has been shown to cause lipid and protein peroxidation. The resulting toxic products contribute to neuronal death [36].

The only drugs that have been shown to produce statistically significant improvements in cognitive performance and in the activities of daily living in large multi-centre placebo-controlled trials in AD subjects are ChE inhibitors [37-39]. They are also effective in treating cognitive impairments in vascular dementia [40]. ChE inhibitors may do so by a combination of increasing cholinergic transmission in the affected cortical areas and by improving their blood supply [41, 42] and glucose metabolism [43]. ChE inhibitors, tacrine, rivastigmine and donepezil have also been reported to reduce delusions, aggressive and paranoid behaviour in subjects with AD and DLB [39, 44, 45] but they do not ameliorate extrapyramidal or depressive symptoms. On the other hand, many effective anti-depressants are cholinergic receptor antagonists and can exacerbate memory impairments in demented patients and antagonize the beneficial effects of ChE inhibitors [46]. However, these drugs do not possess the neuroprotective and neurorescue activity of the anti-PD drug, rasagiline.

In order to treat the cognitive, extrapyramidal and depressive symptoms of dementia, we have prepared a new drug, ladostigil, (N-propargyl-(3R)-aminoindan-5-yl-ethyl methyl carbamate, hemitartrate) in which the carbamate moiety of rivastigmine was introduced into the 6 position of the rasagiline molecule to provide ChE-inhibitory activity [47] and neuroprotective activity of rasagiline. This resulted in a reduction of approximately 5 orders of magnitude in the MAO-B inhibitory activity *in vitro* compared to that of rasagiline. However, on repeated oral administration of ladostigil to rats and mice, MAO-A and -B inhibition in the brain was seen at similar doses to those which inhibited ChE and these were much lower than would be expected from the poor *in vitro* activity [47]. The difference between the in vitro and *in vivo* MAO inhibitory activity has been attributed to the loss of carbamate pseudo inhibitory moiety, with inhibiton of ChE resulting in several propargylamine aminoindan metabolites accumulation in the brain that inhibit MAO-A and -B. In contrast, M30 is a potent propargylamine containing MAO-A and -B inhibitor *in vitro* and *in vivo* [48, 49] and has shown neuroprotective and neurorestorative activities in three classical animal models of PD, namely MPTP [48], lacatcystin [20] and 6-hydroxydopaine (Kupershmidt et al. unpublished) .

EFFECT OF LADOSTIGIL AND M30 ON APP PROCESSING

TV-3326 and rasagiline have been shown to stimulate the processing of APP by α-secretase to the neuroprotective soluble

APP-α in cultured rat phaeochromocytoma (PC12) and human neuroblastoma (SY5Y) cells [50]. This action is not due to ChE or MAO inhibition, but occurs through activation of protein kinase as a result of the presence in the molecule of the propargylamine moiety. If this also occurs in the brain of AD patients it should reduce the abnormal processing of APP to the neurotoxic β-amyloid by β and γ-secretases and the likelihood of forming amyloid plaques.

NEUROPROTECTIVEAND NEURORESCUE ACTIVITIES OF LADOSTIGIL AND M30

Ladostigil and M30 [5-(N-methyl-N-propargyaminomethyl)-8-hydroxyquinoline] have many of the neuroprotective actions of rasagiline in cultured neuronal cells. These include prevention of the fall in the mitochondrial potential and cytotoxicity in SY5Y and PC12 cells in response to oxidative stress induced by peroxynitrite or glucose oxygen deprivation [15, 51]. It also shows neuroprotective activity *in vivo*, significantly reducing hippocampal cell damage induced by global ischemia in gerbils and the cerebral oedema induced in mice by closed head injury [15, 52]. Rivastigmine, a ChE inhibitor, which does not show the neuroprotective actions of TV-3326 against oxidative stress *in vitro*, nevertheless hastens the recovery if brain injured mice from motor and memory impairments. This indicates that the ability of TV-3326 to maintain cholinergic transmission is an important attribute in the treatment of brain trauma in addition to its anti-apoptotic actions [52, 53]. The neuroprotective effects against oxidative stress may enable ladostigil to delay the progression of AD and DLB. As a ChE inhibitor, the drug could increase cortical cholinergic activity and improve attention and cognitive function. It could also provide symptomatic improvement of extrapyramidal symptoms by increasing nigrostriatal dopamine transmission. Since drugs that inhibit both MAO-A and -B are effective anti-depressants in human subjects it is likely that ladostigil will also display this activity. These actions are reported in more detail below.

Novel therapeutic approaches for the treatment of neurodegenerative disorders comprise drug candidates designed specifically to act on multiple CNS targets. We have synthesized a multifunctional non-toxic, brain permeable iron chelator drug, M-30, possessing propargyl MAO inhibitory neuroprotective and iron-chelating moieties, from our prototype iron chelator VK-28. M-30 was shown to possess a wide range of pharmacological activities, including pro-survival neurorescue effects, induction of neuronal differentiation and regulation of APP and beta-amyloid (Aβ) levels. M-30 was found to decrease apoptosis of SH-SY5Y neuroblastoma cells in a serum deprivation model, via reduction of the pro-apoptotic proteins Bad and Bax, and inhibition of the apoptosis-associated phosphorylated H2A.X protein (Ser 139) and caspase-3 activation. In addition, M-30 induced the outgrowth of neurites, triggered cell cycle arrest in G(0)/G(1) phase and enhanced the expression of growth associated protein-43. Furthermore, M-30 markedly reduced the levels of cellular APP and beta-C-terminal fragment (beta-CTF) and the levels of the amyloidogenic Abeta peptide in the medium of SH-SY5Y cells and Chinese hamster ovary cells stably transfected with the APP 'Swedish' mutation. Levels of the non-amyloidogenic soluble APPalpha and alpha-CTF in the medium and cell lysate respectively were coordinately increased. The ability of theses novel iron chelators to regulate APP is in line with the presence of an iron-responsive element (IRE) in the 5'-untranslated region (5'UTR) of APP. Similarly, M30 reduced the levels of toxic amyloid-beta peptides in CHO cells over-expressing the APP "Swedish" mutation. The novel multi-target iron chelating-radical scavenging compound M30 possesses beneficial effects on major hallmarks of Alzheimer's disease. Systemic treatment of APP/PS1 Tg mice with M30 for nine months, significantly attenuated cognitive impairments in a variety of tasks of spatial learning and memory retention, working memory, learning abilities, anxiety levels, and memory for novel food and nesting behaviour. Furthermore, M30 reduced cerebral iron accumulation accompanied by a marked decrease in several AD-like phenotypes, including cerebral APP levels, Aβ levels and plaques, phospho-APP and phospho-tau. Signaling studies revealed that M30 markedly downregulates the levels of phosphorylated cyclin-dependent kinase 5 and increased protein kinase B and glycogen synthase kinase 3β phosphorylation [54].

The novel multifunctional brain permeable iron, chelator M30 was shown to possess neuroprotective activities *in vitro* and *in vivo*, against several insults applicable to various neurodegenerative diseases, such as AD, PD, and amyotrophic lateral sclerosis (ALS). We demonstrate that systemic chronic administration of M30 resulted in up-regulation of hypoxia-inducible factor (HIF)-1α protein levels in various brain regions (e.g. cortex, striatum, and hippocampus) and spinal cord of adult mice. Real-time RT-PCR revealed that M30 differentially induced HIF-1α-dependent target genes, including vascular endothelial growth factor, erythropoietin, enolase-1, transferrin receptor, heme oxygenase-1, inducible nitric oxide synthase, and glucose transporter-1. In addition, mRNA expression levels of the growth factors, BDNF and GDNF and three antioxidant enzymes (catalase, superoxide dismutase (SOD)-1, and glutathione peroxidase) were

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up-regulated by M30 treatment in a brain-region-dependent manner. Immunoblotting studies revealed that M30 induced a differential enhanced phosphorylation of protein kinase C, mitogen-activated protein kinase (MAPK)/ERK kinase (MEK), protein kinase B (PKB/Akt), and glycogen synthase kinase-3β (GSK-3β). Together, these results suggest that the multifunctional iron chelator M30 can up-regulate a number of neuroprotective-adaptive mechanisms and pro-survival signalling pathways in the brain that might function as important therapeutic targets for the drug in the context of neurodegenerative disease therapy [55]. These properties, together with its brain selective MAO inhibitory and propargylamine- dependent neuroprotective effects, suggest that M-30 might serve as an ideal drug for neurodegenerative disorders, such as AD and PD, in which oxidative stress and iron dysregulation have been implicated.

CHOLINESTERASE INHIBITION BY LADOSTIGIL

The inhibition by ladostigil of AChE and butyrylcholinesterase (BuChE) *in vitro* was tested by preincubating the respective enzymes with the drug for different periods of time. It was found that ladostigil caused a slowly developing inhibition of both enzymes but was about 100 times more potent against BuChE than AChE (Fig. 1). This may be an advantage over an AChE-selective inhibitor, since the levels of BuChE do not decline like those of AChE in the brains of AD patients and its inhibition can contribute to the maintenance of acetylcholine (ACh) levels in the synaptic gap [56]. After oral administration to rats, ladostigil inhibited cortical ChE (comprised of about 90% AChE and 10% BuChE) by 20-80% at doses ranging from 9-200 mg/kg [52]. Ladostigil (12-26 mg/kg) caused a dose-related antagonism of the spatial memory deficits induced by scopolamine in rats, indicating that it was able to increase brain ACh levels sufficiently to compete with scopolamine for muscarinic receptors subserving memory [52].

BRAIN SELECTIVE INHIBITION OF MAO IN RESPONSE TO ADMINISTRATION OF LADOSTIGIL AND M30

In order to inhibit MAO-A and -B in the brain of rats by 50% after acute oral administration of ladostigil, it was necessary to give a dose of at least 120 mg/kg. However, once daily administration for 2 weeks of a smaller dose of ladostigil (26 mg/kg) inhibited brain MAO-B by 71% and MAO-A by 66%, with very little or no effect on these enzymes in the intestine [47, 57]. Treatment of rats with ladostigil for two months resulted in brain MAO inhibition of more than 90% without any appreciable affect on the intestinal enzymes. Furthermore, in rabbits, ladositigil (26 mg/kg) inhibited brain MAO by more than 90% after only two weeks of daily administration, but did not inhibit intestinal MAO-A, which comprises over 80% of the total MAO in this tissue [53]. In view of the fact that ladostigil did not inhibit MAO-A or B *in vitro* at concentrations below 250 μM or 1 mM, respectively, it is likely that the brain-selective effect of the drug results from the local formation of a more active metabolite. Several such metabolites have recently been identified in the blood of rats and monkeys after oral administration of ladostigil. One of these is produced by hydrolysis of the carbamate moiety of ladostigil by ChE to yield the 6-OH derivative. When tested for its activity against MAO-A and -B we found that the concentrations needed to inhibit these enzymes were 0.46 μM and 0.35 μM, respectively, i.e. about 500-600 times more active than ladostigil. It remains to be determined whether adequate concentrations of this metabolite are present in the brain after chronic oral administration of ladostigil such as to produce significant brain-selective MAO inhibition.

LIMITED POTENTIATION BY LADOSTIGIL AND M30 OF CARDIOVASCULAR RESPONSE TO TYRAMINE

The finding that ladostigil caused little or no MAO-A inhibition in the intestine suggested that patients receiving the drug should show a much smaller increase in blood pressure on ingestion of tyramine-containing foods or beverages than those treated with other irreversible, non-selective MAO-inhibitors, like iproniazid and tranylcypromine. This possibility was tested in conscious rabbits receiving tyramine by oral administration [58]. It was found that after chronic treatment of rabbits with ladostigil, tyramine only increased blood pressure by 30 mm Hg at doses exceeding 30 mg/kg, compared to about 60-70 mg/kg in untreated animals. In human subjects this amount is equivalent to about 900 mg, which is much more than would be present in any reasonable amount of tyramine-containing food or beverage [59]. By contrast, a 30 mmHg increase in blood pressure was achieved with only 2 mg/kg of tyramine in rabbits treated with tranylcypromine (20 mg/kg), which inhibited brain MAO-A and -B to a similar extent to ladostigil but caused more than 90% inhibition of intestinal MAO [58].

INCREASE IN NIGROSTRIATAL DOPAMINE NEUROTRANSMISSION AND NEUROPROTECTION

Dopamine is a substrate for both MAO-A and -B. While rat and mouse brain contains about equal proportions of these

enzymes, the extrapyramidal region of the human has about 4 times more MAO-B than -A [60, 61]. This was one reason why Birkmayer and his colleagues [2, 3] introduced the MAO-B inhibitor selegiline, as therapy in PD subjects to potentiate the pharmacological actions of L-DOPA. The potential role of extrapyramidal MAO-B in the pathology of PD was strengthened by the discovery that extrapyramidal symptoms could be induced by the neurotoxin MPTP, which is inert, but can be metabolized by MAO- B in striatal microglia to the toxic metabolite, MPP^+ [62]. The latter is then taken up by striatal dopamine nerve endings and causes their degeneration by oxidative stress [63]. MAO-B inhibitors protect against MPTP neurotoxicity by preventing its conversion to MPP^+ [63, 64]. However, they may also reduce the neuronal damage produced by MPP^+ by an action independent of MAO-B blockade [63, 65]. Since ladostigil has protective actions against oxidative stress in addition to inhibiting MAO-B, we tested its effect in the MPTP mice model of PD to see if like other propargylamine-containing compounds it could prevent degeneration of nigrostriatal dopamine neurons [66]. It was found that chronic, once daily administration of ladostigil (26 mg/kg) for 14 days that inhibited brain MAO-A and B by 70 % completely prevented the depletion of striatal dopamine and the reduction in its metabolites, DOPAC and HVA by MPTP. Since ladostigil also inhibited MAO-A, it increased brain levels of serotonin and noradrenaline. These findings suggest that like selegiline, ladostigil may have therapeutic value in treating the extrapyramidal symptoms in AD and DLB. M30 being a potent brain selective MAO A and B inhibitor *in vivo* produces similar effect on increased brain levels of dopamine, serotonin and noradrenaline as that of ladostigil and is neuroproective not only in the MPTP animal model of PD but also in lacatcystin and 6-OHDA animal models.

ANTIDEPRESSANT ACTIVITY OF LADOSTIGIL AND M30

A popular screening test in rats for potential antidepressant drugs is the forced swim, or "Porsolt test" in which rats are confined on two consecutive days to a narrow cylinder of water, for 15 and 5 min, respectively. After initial attempts at swimming and struggling they develop a form of "learned helplessness" indicated by immobility, which is manifest for more than 70% of the time of exposure on the second day. Pre-treatment with a variety of different antidepressant drugs including MAO-A inhibitors, tricyclics, serotonin uptake inhibitors and others, reduces the duration of this immobile behaviour [67, 68]. We found that daily administration of ladostigil, 26 mg/kg/day for two weeks, or 52 mg/kg for one week, both of which inhibited brain MAO-A and -B by more than 65%, significantly reduced the time of immobility and was similar to the effect seen after chronic treatment with amitriptyline (10 mg/kg/day) and moclobemide (20 mg/kg/day), a reversible MAO-A selective inhibitor [57]. In rats showing this antidepressant-like effect of ladostigil, there was a significant increase in the brain levels of serotonin [58]. A similar result was also obtained with M30 in the same animal model with 5 mg/kg given orally for 3 weeks (Kupershmidt et al unpublished data).

CONCLUSION

Ladostigil and M30 are multi target, so called, "dirty" drugs that were designed to answer the therapeutic requirements of progressive neurodegenerative diseases with features of dementia, behavioural abnormalities, depression and extrapyramidal symptoms in PD and AD. Ladostigil inhibits AChE/BuChE and shows significant antagonism in rats of memory impairment induced by scopolamine and has a larger therapeutic ratio than other ChE inhibitors currently in use for the treatment of AD [47, 52]. M30 has highly significant cognitive enhancement in double transgenic Swedish mutation/PSI1 mice [69]. A unique feature of these drugs is their ability to produce brain-selective inhibition of both MAO-A and -B in rats, mice and rabbits . This property enables the drugs to exert antidepressant activity like that of amitriptyline and moclobemide without causing any clinically significant potentiation of the pressor response to oral tyramine. Since the neurodegeneration in AD and PD is associated with oxidative stress and impairment of mitochondrial function, an additional advantage of these drugs is their ability to reduce apoptosis and the fall in mitochondrial membrane potential resulting from oxidative stress in neuronal cell cultures. Both have also been shown to stimulate the processing of APP to the neuroprotective soluble APPα, thereby reducing the likelihood of its processing to toxic Aβ, a key player in the progression of AD. These latter actions probably result from direct activation of protein kinase C and do not involve either ChE or MAO-inhibition. These unique multiple properties of ladostigil and M30 make them potentially useful drugs for the treatment of dementia with Parkinsonian-like symptoms and depression. A recent double blind control study with ladostigil in AD subjects has already shown positive results.

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