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Research Report

Neuroprotection by rasagiline in thiamine deficient rats

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ABSTRACT

Thiamine deficiency (TD) in rats is a model of chronic impairment of oxidative metabolism leading to neuronal loss. TD rats exhibit neuropathological, behavioral and cognitive abnormalities. The aim of this study was to use this syndrome to assess the neuroprotective potential of drugs in a whole animal model. TD was produced in rats using the following protocol: thiamine deficient diet, daily injections of the central thiamine antagonist, pyrithiamine (0.5 mg/kg), and the test drugs, the selective monoamine oxidase (MAO) B inhibitors, rasagiline (1 or 3 mg/kg/day) and selegiline (2.4 or 8 mg/kg/day). Normal rats and untreated TD rats served as controls. Upon the appearance of neurological symptoms, the TD protocol was suspended, rats were transferred to a regular diet, pyrithiamine and test drug injections were terminated and rats were injected with 3 daily doses of thiamine (100 mg/kg). Neuroprotective potential was assessed by: general behavioral observations, cognitive testing using the Morris water maze and histopathological examination of the brains. Rasagiline but not selegiline significantly delayed the onset and severity of the neurological symptoms of TD. In the Morris water maze, TD-untreated rats displayed severe cognitive impairment while rasagiline-treated rats were similar to control rats and significantly different from TD-untreated rats. The effects were dose related. Selegiline treatment had no significant protective effect. TD-untreated brains displayed extensive gliotic and necrotic lesions mainly in the thalamus and posterior collicular nucleus, which were significantly reduced in the rasagiline-treated TD rats. These findings demonstrate significant neuroprotection by rasagiline with possible implications for clinical neurodegenerative disorders.

1. Introduction

Thiamine (vitamin B_1) as pyrophosphate is an essential cofactor for the mitochondrial enzymes α-ketoglutarate dehydrogenase complex, transketolase and pyruvate dehydrogenase complex (Gibson et al., 1984; Butterworth et al., 1986; Giguère and Butterworth, 1987). Thiamine deficiency (TD) severely affects the activity of these enzymes, inhibiting the conversion of pyruvate into acetyl CoA and α-ketoglutarate into succinate (Bubber et al., 2004). The α-ketoglutarate dehydrogenase complex is a key and rate-controlling enzyme of the citric acid cycle and is reduced in neurodegenerative diseases (Gibson et al., 2005, 1999; Gibson and Zhang, 2002). Inactivation of this enzyme by factors elevated in oxidative stress such as H_2O_2 and peroxynitrite supports its role in degenerative processes.

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Abbreviations: GFAP, Glial fibrillary acidic protein; HE, Hematoxylin and eosin stains; IP, Intraperitoneal; MAO, Monoamine oxidase; MPTp, Mitochondrial permeability transition pore; SC, Subcutaneous; SHR, Spontaneously hypertensive rats; TD, Thiamine deficiency; WKS, Wernicke–Korsakoff syndrome

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Table 1 – Effect of propargylamine drugs on the initiation of the symptoms of TD (Series 1, 9 month-old rats)

Proportion of rats exhibiting loss of righting reflex

Groups	Time from initiation of thiamine deprivation (days)					
	12	13	14	15	16	17
TD-untreated	2/12	9/12	12/12	12/12	12/12	12/12
TD-rasagiline (1 mg/kg)	0/12	2/12	8/12	9/12	9/12	9/12
TD-selegiline (8 mg/kg)	0/12	6/12	12/12	12/12	12/12	12/12

The neurological disorder most clearly associated with TD in humans is the Wernicke–Korsakoff syndrome (WKS). It is a behaviorally and pathologically heterogenous disorder most commonly observed in malnourished, chronic alcoholics. Patients display deficits in neuropsychological tests ranging in severity from spared cognitive ability to amnesia with mild to moderate cognitive deficits to dementia. Thinning of the cortex and loss of white matter are often seen and are attributed to heavy alcohol consumption.

Lesions in the medial thalamus and mammillary bodies are also common and are attributed to TD. These diencephalic lesions damage nuclei and tracts of memory systems causing the amnesia in WKS (Langlais and Savage, 1995).

The most common animal model of TD and WKS is the nonsurgical rodent model termed pyrithiamine-induced TD (Troncoso et al., 1981). In this model, rats are free-fed thiamine deficient chow and given daily injections of pyrithiamine hydrobromide. Pyrithiamine inhibits thiamine metabolism as well as its blood–brain transport (Rindi et al., 2003) resulting in a sequence of neurological disturbances, such as ataxia and inhibition of the righting reflex, which are alleviated only when thiamine is restored (Pitkin and Savage, 2001). The range of chronic brain lesions is very similar to those of WKS (Langlais et al., 1996).

Rasagiline, N-propargyl-1-(R) aminoindan mesylate is used for the symptomatic treatment of Parkinson's disease (Parkinson Study Group 2002, 2004). Its predecessor is selegiline which shares with it the propargylamine structure. Both rasagiline and selegiline are selective MAO-B inhibitors, thus providing the rationale for their use in Parkinson's disease (Finberg et al., 1999). Rasagiline is metabolized to aminoindan (Chen and Swope, 2005), which has demonstrated neuroprotective activity (Bar Am et al., 2004) while selegiline is metabolized to neurotoxic L-methamphetamine (Abu-Raya et al., 2002; Reynolds et al., 1978).

Selegiline was investigated as a disease-modifying agent in several models of evoked neuropathy including thiamine deficient rats (Todd and Butterworth, 1998) and showed varying levels of neuroprotection (Seniuk et al., 1994; Tatton et al., 1994; Semkova et al., 1996; Mytilineou et al., 1997). In long-term disease modification of Parkinson's disease, beneficial effects were demonstrated (Stocchi and Olanow, 2003; Fernandez and Chen, 2007). However the mechanism has not been resolved.

Rasagiline has been evaluated as a neuroprotective agent in several whole animal rodent models. In permanent focal ischemia in the rat, it decreased infarct size and restored motor function (Speiser et al., 1999, 2007). It restored cognitive function in post-natal anoxia lesioned rats, as well as in adult and senescent hypoxia lesioned rats (Speiser et al., 1998a,b). In spontaneously hypertensive rats (SHR), it prevented spontaneous hypothalamic cell death (Eliash et al., 2005). In stroke-prone SHR, it increased survival and delayed or prevented the incidence of stroke (Eliash et al., 2001). In closed head injury in mice, it restored motor and cognitive function (Huang et al., 1999) as well as in a transgenic model of multiple system atrophy (Stefanova et al., 2008).

Mechanism-oriented studies have also been performed in various cell cultures (Abu-Raya et al., 1999; Maruyama et al., 2001a, 2002a; Yi et al., 2006). Rasagiline and related propargylamines suppressed the apoptotic cell death cascade initiated at the mitochondria (Akao et al., 2002a). The proapoptotic decline in mitochondrial membrane potential was prevented and the following apoptotic processes were inhibited: activation of caspase-3; nuclear translocation of glyceraldehyde-3-phosphate dehydrogenase; and nucleosomal DNA fragmentation (Maruyama et al., 2001a,b; 2002b; Youdim and Weinstock, 2002). In addition, rasagiline increased the expression of

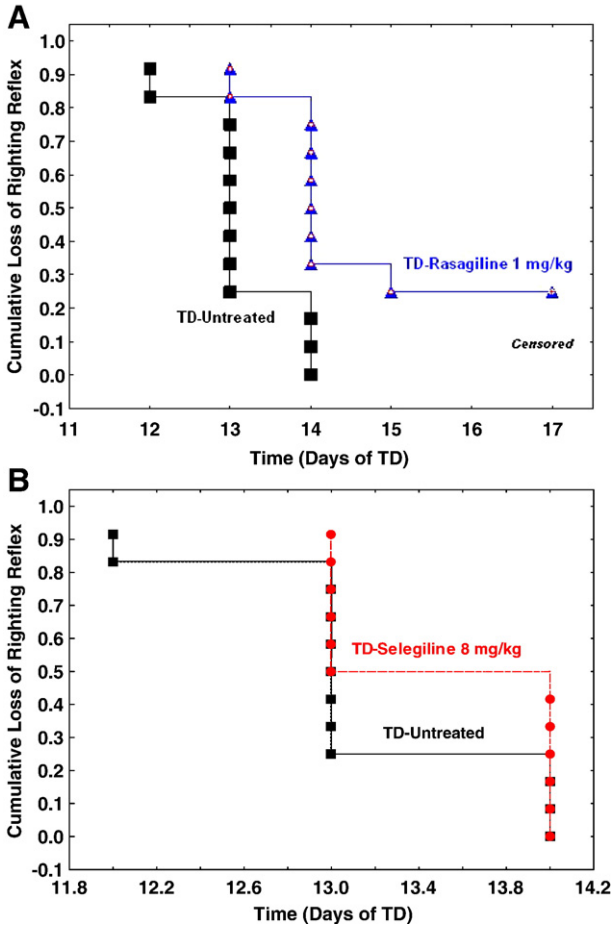

Fig. 1 – Series 1 (9 month-old rats). Kaplan Meier survival plot of the effect of rasagiline (A) and selegiline (B) on inhibition of righting reflex censored for 17 days. Censored data are the cases where the loss of righting reflex was longer than the observation period. Comparing TD-rasagiline and TD-untreated rats, Sig. $p=0.002$, Log Rank (Mantel-Cox) 9.76; TD-selegiline and TD-untreated, Sig. 0.125, Log Rank 2.35; TD-selegiline and TD-rasagiline Sig. 0.017, Log Rank 5.72.