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Characteristics of Neuronal Dysfunction induced by Thiamine-Deficient Feeding

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Thiamine deficiency (TD) leads to the conditions known as beriberi, and Wernicke-Korsakoff's syndrome (WKS), characterized by selective cell loss, cholinergic deficits and profound memory loss. These changes also occur in Alzheimer's disease (AD). Treatment with high doses of parenteral thiamine generally leads to the prompt clinical improvement of beriberi and Wernicke's encephalopathy. It is also reported that the progress of dementia in AD patients can be halted by a timely injection of a bolus dose of thiamine. Lack of appropriate treatment is often lethal and delayed treatment is followed by subsequent serious symptoms. Therefore, it is imperative to precisely elucidate the mechanism of learning and memory impairment induced by TD.

There are two types of experimental models of TD: antithiamine- and dietary-induced TD. In this review article, we propose the roles of the cholinergic and somatostatinergic systems in the brain in learning and memory impairment in

dietary-induced TD, based on our findings of behavioral testing and immunohistochemical analysis.

Dietary-induced TD causes various abnormal behaviors in rats and mice (Table 1). The escape behavior and increased startle response appear during the early stage of a TD diet (Onodera et al., 1978a). After 12-14 days of TD treatment, bradycardia (Onodera et al., 1991), lack of appetite (Onodera et al., 1981) and hypothermia (Onodera et al., 1990) appear. Persistent erection (Onodera et al., 1978), hypotension (Onodera et al., 1991), increased pain threshold (Nakagawasai *et al.*, 2001b; Tadano *et al.*, 1999; Tadano *et al.*, 1995), muricide (mouse-killing behavior) (Tadano *et al.*, 1997), impairment of learning and memory (Nakagawasai *et al.*, 2001a; Nakagawasai *et al.*, 2000a and b), increased immobility time on the forced swimming test (Nakagawasai *et al.*, 2001c) and altered circadian rhythm are observed during the late stage (20-30 days) of a TD diet. Among the above-mentioned behaviors, muricide, increased pain threshold, impairment of learning and memory and increased immobility time, once they appear, cannot be suppressed by an injection of thiamine HCl. These findings indicate that these responses may result from irreversible change(s) in certain brain or spinal regions caused by TD.

Learning and memory impairment as determined by passive avoidance task was

observed on the 20-25th day in dietary-induced TD rats and mice (Fig. 1). Antithiamine-induced TD has also been demonstrated by the water maze task, T-maze task, a nonmatching-to-sample task and matching to sample task. These results have been suggested that TD induces a working memory impairment in rodents. This type of working memory impairment has been seen in aged humans and in WKS patients. We have investigated the effect of cholinergic drugs on the impairment of learning and memory in rats and mice after TD feeding. The impairment of learning and memory was improved by administration of chronic physostigmine (intraperitoneally; i.p.), a cholinesterase inhibitor (Nakagawasai *et al.*, 2000b), and oxotremorine (i.p.), a non-selective muscarinic agonist (Nakagawasai *et al.*, 2001a). However, administration of lobeline (i.p.), a nicotinic agonist, did not reverse the learning and memory impairment (Nakagawasai *et al.*, 2001a). Another group has also reported that in antithiamine-induced TD animals the performance in the string test (standardized test of neurological competence that measures ability to traverse a string) was reversed by injection of physostigmine and arecholine, a muscarinic agonist, but not by nicotine. Moreover, we examined the role of muscarinic receptor subtypes on the learning and memory impairment induced by TD feeding. Stimulation of postsynaptic muscarinic M_1 and inhibition of presynaptic M_2 receptors can enhance the acquisition of

spatial reference memory in both the water maze test and non-matching to position test. Intracerebroventricular (i.c.v.) administration of McN-A-343, a muscarinic M_1 receptor agonist, improved the learning and memory impairment in TD mice. Interestingly, methoctramine (i.c.v.), a selective muscarinic M_2 receptor antagonist, did not have a significant effect on TD-induced learning and memory impairment (Nakagawasai *et al.*, 2001a). It has been demonstrated that the intensity of choline acetyltransferase (ChAT) fluorescence, a marker of presynapse of cholinergic neurons, is decreased in the cortex, hippocampus and thalamus in the late stage in TD rats. These findings suggest that methoctramine dose not have a positive effect on the impairment of memory function since the presynaptic cholinergic neurons were degenerated after a TD diet. Muscarinic M_2 receptors play an important role in an irreversible change model of impairment of learning and memory induced by TD feeding.

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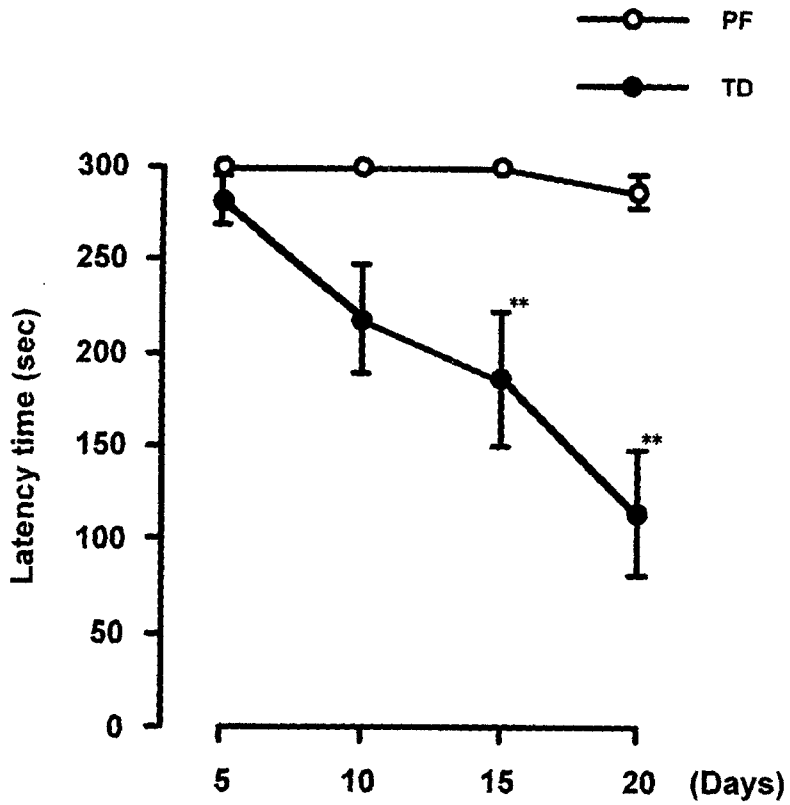

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Fig. 1 Effects of avoidance behavior after starting thiamine deficient feeding, as measured by a passive avoidance task. **p<0.01, significant difference between PF and TD. N=10 per group.

Table 1 Abnormal behaviors induced by thiamine deficiency

Behaviors	References
Increased startle response	Onodera et al., 1978a
Bradycardia	Onodera et al., 1991
Lack of appetite	Onodera et al., 1981
Hypothermia	Onodera et al., 1990
Persistent erection	Onodera et al., 1978b
Hypotension	Onodera et al., 1991
Increased muricidal behavior	Tadano et al., 1997
Increased pain threshold	Tadano et al., 1995 and 1999; Nakagawasai et al., 2001b
Learning and memory deficits	Nakagawasai et al., 2000a, b and 2001a
Depressive behavior	Nakagawasai et al., 2001
Altered circadian rhythm	Bennett and Schwartz, 1999