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Acute effects of high-dose thyrotropin releasing hormone infusions in Alzheimer's disease

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Abstract. Thyrotropin releasing hormone (TRH) was administered intravenously to ten patients with Alzheimer's Disease (AD) in a high-dose paradigm, thought to maximize central nervous system effects and potentially produce facilitation of cholinergic function, a known property of the neuropeptide. Acute effects of TRH on behavioral, cognitive and physiologic measures were assessed after patients received 0.1 mg/kg TRH, 0.3 mg/kg TRH and placebo, the higher TRH dose and placebo being given in a randomized, double-blind fashion. Patients showed statistically significant increases in arousal and improvement in affect, as well as a modest improvement in semantic memory, all after receiving the higher TRH dose. Both TRH doses produced transient rises in systolic blood pressure, with no effect on diastolic blood pressure, heart rate or temperature. This study suggests that high-dose TRH can be safely administered to AD patients and is neurobehaviorally active; further studies are needed to determine the extent and mechanism of the cognitive and psychobiological properties of this peptide in AD and other neuropsychiatric disorders.

Key words: Thyrotropin releasing hormone – Alzheimer's Disease – Neuropeptides

In addition to its role in the regulation of thyroid function, thyrotropin releasing hormone (TRH) has long been recognized as a modulatory neuropeptide, with a broad spectrum of central nervous system (CNS) activity (Griffiths 1985; Horita et al. 1986). Abundant extra-hypothalamic TRH receptors have been demonstrated in both rodent (Pazos et al. 1985) and human brain (Manaker et al. 1986), and while considerable animal data has accumulated concerning the brain effects of TRH, little is known of the central consequences of TRH action in humans. Although TRH interacts with several classical neurotransmitters, the most robust evidence is for a positive modulatory effect of TRH on the action of acetylcholine (Ach) in the CNS (Breese et al. 1975; Yarbrough 1976; Schmidt 1977; Yarbrough and Singh 1977; Kalivas and Horita 1980; Pirola et al. 1983; Yarbrough 1983). Alzheimers Disease (AD) is a neuropsychiatric disorder characterized clinically by progressive dementia; a prominent neurochemical feature of the illness is a loss of cortical markers for presynaptic Ach and a degeneration of cholinergic pathways; such cholinergic loss appears to correlate with clinical severity of the dementia (Davies and Maloney 1976; Whitehouse et al. 1982; Sims et al. 1983). In addition, TRH levels have been reported to be decreased in the cerebrospinal fluid of dementia patients (Oram et al. 1981), although not in post-mortem brain tissue (Yates et al. 1983). Because of its known positive neuromodulatory effects on cholinergic transmission, we chose to examine, in a pilot fashion, the acute behavioral, cognitive and physiologic effects of TRH in a group of patients with AD in an effort to explore whether a 'neuromodulatory' strategy was feasible in this illness, as has previously been suggested (Yarbrough and Pomara 1985).

TRH has been reported to have antidepressant properties (Kastin et al. 1972; Prange et al. 1972) and to be beneficial in schizophrenia (Wilson et al. 1973a; Inanaga et al. 1978); these results have not been consistently replicated and remain controversial (Davis et al. 1975; van den Burg et al. 1976). A major limitation of previous psychopharmacologic studies with TRH, including one small study with AD patients (Peabody et al. 1986), has been the use of doses which, although high enough to maximally stimulate pituitary function, are probably too low to gain sufficient CNS access to produce neurobehavioral effects (Nagai et al. 1980; Sunderland et al. 1986). TRH is extremely labile in the circulation (Bassiri and Utiger 1973), owing to active enzymatic degradation (Redding and Schally 1969). Animal studies suggest that the doses required to produce behavioral effects are 10–100 times higher than those which maximally evoke thyroid stimulating hormone (TSH) release (Metcalf 1982). In this pilot study, therefore, we have administered TRH in intravenous doses up to 40 times those given previously in psychopharmacologic and endocrine studies of psychiatric patients, in hopes of achieving sufficient brain levels to observe central effects of TRH. A preliminary version of this work has been previously reported in abstract form (Mellow et al. 1987).

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Methods

Ten patients (five males, five females; mean age 64.3 ± 2.2 years) were studied while inpatients on the NIMH Unit on Geriatric Psychopharmacology. All patients met DSM-III-R criteria for Primary Degenerative Dementia of the Alzheimer Type (American Psychiatric Association 1987) as well as NINCDS-ADRDA criteria for "probable" Alzheimer's Disease (McKhann et al. 1984). Mean duration of illness was 4.1 ± 0.5 years and the mean Global Deterioration Scale (Reisberg et al. 1982) severity index was 4.6 ± 0.3, indicating moderate dementia. Patients were without serious medical illness or coexistent psychiatric disorder, and had received no psychoactive drugs for at least 3 weeks prior to the study. Patients underwent 3 separate study days (at least 72 h apart) as follows: On day 1, every patient received TRH, 0.1 mg/kg, under single-blind conditions. On days 2 and 3, patients received TRH, 0.3 mg/kg or placebo, in a randomized fashion. Both patients and physician-investigator were blind to drug/placebo conditions on days 2 and 3. The first day of single-blind infusion was included, since the safety of high doses of TRH in this population had not been established; an initial dose of 0.1 mg/kg was chosen to detect patients who might have unusual sensitivity to the peptide. Every patient completed all 3 days of the protocol.

After an overnight fast, TRH or saline placebo was administered through an inwelling intravenous catheter as a bolus infusion over 1 min. Behavioral measures were made 30 min prior to drug infusion and 30 and 90 min after infusion and included: (1) Brief Psychiatric Rating Scale (BPRS; Overall and Gorham 1962), (2) an observer-rated 100 mm Visual Analog Scale (VAS) for assessment of arousal, affect, motor behavior, orientation and verbal expression, designed to assess potential behavioral effects of cholinergic enhancement (Tariot et al. 1988), and (3) Modified NIMH Self-Rating Scale (van Kammen and Murphy 1975). The cognitive battery was administered along with the behavioral ratings and included: (1) *vigilance task* (measure of attention) – patients were read a list of 18 words, of which 6 were read once and 6 read twice, and were asked to note any repeated word; (2) *category retrieval* (measure of semantic or "knowledge" memory) – patients were asked to generate related words over a 90-s period in response to a category stimulus (Bättig and Montague 1969; Tariot et al. 1988); (3) *picture recognition task* (measure of visual memory) – patients were shown ten simple pictures and, after a distractor task, shown the original pictures interspersed with ten new pictures and asked to identify old and new pictures; (4) Buschke *selective reminding task* (Buschke 1973) (measure of episodic verbal memory) – this task was modified for use with AD patients by decreasing the test word list from 12 to 6 words (Sunderland et al. 1987). Two patients were unable to complete the cognitive battery due to the severity of their dementia at baseline; cognitive measures are reported for the remaining eight patients. Blood pressure and heart rate were measured at 5-min intervals using an automated vital signs monitor (Critikon Inc., Tampa, FL), and oral temperature was measured at 30-min intervals.

Data were analyzed with SAS statistical software (Cary, NC) by analysis of variance (ANOVA) with repeat measures; Pearson product-moment correlation coefficients were calculated for correlation of behavioral with physiologic data. Analyses were done without regard to order of drug presentation. Post hoc paired *t*-tests were performed on difference scores when the overall ANOVA showed an interaction (difference scores are reported for clarity of presentation; ANOVAs revealed no significant baseline differences across treatment conditions). Significance was at the $P = 0.05$ level. TRH was purchased from Peninsula Laboratories (Belmont, CA) and analyzed for purity with high pressure liquid chromatography by the NIH Pharmaceutical Development Service.

Results

Physical effects. All patients tolerated the infusions without major adverse reactions. Most experienced transient shivering, urinary urgency and hot and cold cutaneous sensations, which lasted about 5 min, primarily after receiving the higher TRH dose. No patients experienced nausea or vomiting.

Behavioral measures. The results of the behavioral measurements are summarized in Table 1. In the majority of instances, when a significant behavioral effect occurred, it was detected by ratings obtained 30 min after drug infusion. The observer-rated Visual Analog Scales (VAS, Table 1 A)

Table 1. Behavioral effects of high-dose TRH infusions in AD patients ($n = 10$). Patients were rated 30 min before and 30 and 90 min after drug/placebo infusions. Each value represents mean ± SEM for the maximal change from baseline measurement for each treatment condition. *P* values refer to post hoc paired *t*-tests on difference scores for those conditions showing an interaction on the ANOVA. In the majority of instances, maximum changes were detected by ratings obtained 30 min after drug infusion.

A

	Placebo	TRH (0.1)	TRH (0.3)
"Flushing"	0.3 ± 1.7	1.9 ± 2.2	0.0 ± 2.0
"Motor Activation"	5.2 ± 2.5	3.7 ± 4.0	9.5 ± 3.1[b]
"Affect"	3.3 ± 4.2	2.1 ± 5.0	14.3 ± 3.3[a]
"Arousal"	1.6 ± 3.0	0.2 ± 4.8	13.0 ± 5.9[a]
"Orientation"	0.2 ± 5.5	5.7 ± 6.7	1.8 ± 5.1
"Expression"	1.3 ± 2.1	4.2 ± 2.6	−0.9 ± 2.5

B

	Placebo	TRH (0.1)	TRH (0.3)
"Activation-Euphoria"	1.8 ± 1.8	5.0 ± 2.6	9.8 ± 4.3[c]
"Altered Self"	0.2 ± 0.6	−1.5 ± 0.7	0.8 ± 1.1
"Anxiety"	1.5 ± 3.5	7.2 ± 5.2	4.0 ± 1.8
"Depressed Affect"	1.0 ± 2.2	−0.8 ± 2.8	−0.5 ± 3.3
"Dysphoria"	0.0 ± 2.5	1.0 ± 1.4	2.3 ± 1.6
"Functional Deficit"	0.6 ± 6.7	−3.0 ± 3.9	5.3 ± 6.3

[a] Significant difference from placebo ($P < 0.05$). b Trend for difference from placebo ($P < 0.15$). [c] Significant change from baseline ($P < 0.02$)

A Effects on Visual Analog Scale (VAS) ratings. Patients were rated by a physician-investigator on six behavioral factors, each measured on a 100 mm line continuum.

B Effects on NIMH Self-Ratings. Patients provided self-ratings on a 24-item questionaire covering various subjective mental states, rated from 0 (not present) to 10 (present in extreme). Subscale analysis of these data yields six behavioral parameters, each with a maximum score of 100

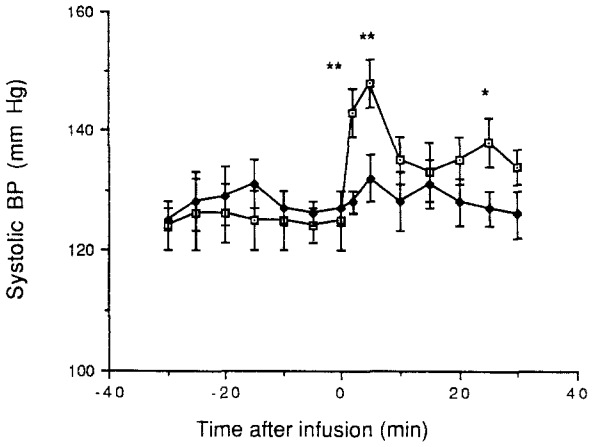

Fig. 1. Effect of high-dose (0.3 mg/kg) TRH infusion on systolic blood pressure (SBP) in AD patients ($n=9$). Blood pressure was measured with an automated cuff system (Critikon) at five minute intervals. ** $P<0.01$, * $P<0.05$, different from placebo. A smaller, but significant rise in SBP was seen after infusion of TRH, 0.1 mg/kg (graph not shown – see text). —□— TRH, 0,3 mg/kg; —●— placebo

showed a significant drug effect ($P<0.05$) for an increase in positive affect and an increase in arousal when patients received the higher (0.3 mg/kg) TRH dose. There was also a significant increase in motor activation (compared to baseline) after the higher dose. These objective behavioral changes were also reflected in a small increase in the self-rating score for the "Activation-Euphoria" subscale on the NIMH Self-Rating Scale (Table 1 B). Overall BPRS scores did not change significantly with either drug dose; however, a subscale analysis of the BPRS showed a trend increase in the "Mania" score with the 0.3 mg/kg dose of TRH compared to placebo (data not shown).

Cognitive measures. No effects of TRH infusions were noted on measures of attention (vigilance task), episodic memory (Buschke task) or visual memory (picture recognition task). There was, however, a statistically significant drug-placebo difference in semantic memory as measured by category retrieval. The 0.3 mg/kg dose of TRH showed a drug-placebo difference of 3.8 ± 1.2 words, in the direction of improvement on drug ($P<0.02$), a 34% difference in change from baseline.

Physiologic measures. TRH produced significant, early, transient systolic blood pressure (BP) elevations at both doses. The means $\pm$ SEM of the maximum rise over baseline in mm Hg were as follows: placebo: 5.1 ± 2.6; TRH, 0.1 mg/kg: 13.4 ± 4.2 ($P<0.05$ different from placebo); TRH, 0.3 mg/kg: 23.4 ± 3.9 ($P<0.01$ different from placebo). The BP response to the higher TRH dose is depicted in Fig. 1. There were no significant effects of TRH infusions on diastolic BP, temperature, or heart rate. There were also no significant correlations between peak change in systolic BP and any behavioral or cognitive measures.

Discussion

This study represents the first attempt to examine the effects of the neuropeptide thyrotropin releasing hormone in AD patients, using an acute infusion paradigm with doses we believe to be high enough to directly affect CNS function. TRH produced a small, acute improvement in mood and increase in arousal and motor activity. One drawback of the current study is the "blindedness" of the design, since many of the patients experienced physical side-effects during active drug infusion. However, several patients had little recall of side-effects during subsequent rating, yet still developed increased arousal, so we believe this phenomenon to reflect a true drug effect. Furthermore, the effects are consistent with those seen in animal studies where TRH can increase locomotor activity (Miyamoto and Nagawa 1977; Masserano and King 1981), as well as in human studies, in which TRH, at lower doses, produced a mild euphoric response (Wilson et al. 1973b, 1980). The mechanisms for these findings are incompletely understood, although it has been suggested that the augmentation of locomotor activity is dopaminergically mediated (Horita et al. 1986) and the effects on arousal may be related to the so-called "analeptic" properties of TRH (Metcalf and Dettmar 1981), with a cholinergic component being prominent (Kalivas and Horita 1980). They are unlikely to be due to stimulation of the thyroid axis, since effects can be seen in hypophysectomized animals (Breese et al. 1975). Moreover, the euphoriant effect of low-dose TRH in humans appears to be negatively correlated with plasma TSH response (Wilson et al. 1973b, 1980), and high doses of TRH do not appear to further stimulate pituitary TSH release in animals (Metcalf 1982) or humans (Mellow, unpublished observations).

The modest cognitive effects of TRH in this study are difficult to interpret; improvement in word generation may be due only to the arousing effects of the drug or to a selective effect on semantic memory function, since measures of attention were unaffected. This study examined only acute effects of the peptide, and it is possible that with chronic administration, more substantial effects on cognition might be observed. For example, in a recent study, Brambilla et al. (1986), demonstrated some cognitive improvement in chronic schizophrenics given daily, low-dose TRH infusions. Finally, it may be that the neurochemical lesions in AD preclude facilitation of cholinergic function; alternatively, the doses used in the present study may be just at or below the threshold for major cognitive effects. In a recent study from our group (Molchan et al. 1988), TRH, at doses even higher than the present study, partially reversed the impairment in new learning induced by the anticholinergic drug scopolamine in normal controls; under these circumstances, when the underlying cholinergic systems are intact, TRH may have positive modulatory effects on memory.

The systolic blood pressure changes seen after TRH infusions in this study are similar in time course and magnitude to those found by Borowski et al. (1984) after 500 µg TRH infusions in a large group of euthyroid patients. A similar rise in blood pressure was also seen by Mitsumoto et al. (1986) during continuous high-dose infusion of TRH to patients with amyotrophic lateral sclerosis. The precise mechanism of the pressor effect of TRH is unknown, although it is thought to involve central stimulation of the sympathetic nervous system (Horita et al. 1986). The lack of correlation of BP changes with behavioral/cognitive changes in this study suggests the possibility of separate mechanisms. It is of interest that we found no significant rise in diastolic BP; in a recent study, the diastolic BP response to TRH in AD patients was significantly blunted

compared with age-matched controls (T.H. Lampe, personal communication). In light of recent evidence for a cholinergic component to the TRH pressor effect (Okuda et al. 1987), these and our own findings might be a reflection of central cholinergic deficits in AD.

In conclusion, in this pilot study, high-dose intravenous TRH could be administered safely to AD patients. The behavioral and physiologic changes seen were similar to those found in earlier studies with much lower doses in normal controls. It remains to be determined whether even higher doses will produce more pronounced or qualitatively different findings, since the doses used in the present study may only be at the threshold for significant central action (Metcalf 1982). Cognitive changes were minimal, but suggested a small, positive effect on semantic memory. Further work is needed with this and other patient populations, as well as with normal controls, to determine the parameters of dosage as well as the extent and mechanisms of the psychobiological actions of TRH in humans. Finally, the present study provides a basis for further investigations into the role of this neuropeptide in the possible pharmacological treatment of the behavioral changes seen in AD.

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