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Cardiovascular, Catecholamine and Psychological Responses to TRH in Four Types of Affective Disorder Patients

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Summary

When 500 ug of TRH is given intravenously, an increase in TSH, blood pressure, plasma catecholamines and positive emotions follows. Four groups of patients with major, minor or bipolar depression or schizoaffective disorder increased their TSH levels by similar amounts after TRH. The neurohormone also significantly increased diastolic blood pressure by 5.5 ± 1.6 mm Hg, and decreased heart rate by 7.6 ± 1.3 beats/min. There was a weak trend for bipolar depressives to have less cardiovascular response to TRH than the other groups.

Plasma norepinephrine (NE) was higher after TRH than after placebo. The NE response differed between patient groups ($P = .0023$) because of a smaller response by major depressives.

TRH decreased anger, tension and depression, and increased friendliness. Positive emotional responses were significantly greater in the bipolar depressives than in other groups.

Forty-one other studies have found a subnormal TSH response does not distinguish between subtypes of the affective disorders, but cardiovascular, catecholamine and mood responses may do so.

Key-Words: *TRH – Thyrotropin Releasing Hormone – Cardiovascular – Catecholamine – Norepinephrine*

Introduction

Thyrotropin releasing hormone (TRH) was first described as a hypothalamic neurohormone which helps regulate the release of thyroid stimulating hormone (TSH) (*Burgus, Dunn, Desiderio* and *Guillemin* 1969). It is also present in many other parts of the brain (*Jackson* and *Reichlin* 1974) where it may function as a neurotransmitter or neuromodulator. High affinity saturable TRH binding sites are present in most areas of rat brain except the cerebellum (*Burt* and *Snyder* 1975), and TRH synthesis occurs in brain areas other than the hypothalamus (*Grimm-Jorgensen* and *McKelvey* 1974). In addition to releasing TSH, systemically administered TRH modifies many cardiovascular, neurochemical and behavioral processes. In animals it increases blood pressure, heart rate (*Tsay* and *Lin* 1982), and plasma catecholamine levels (*Brown* 1981), increases turnover of norepinephrine (NE) (*Keller, Bartholini* and *Pletscher* 1974); *Rastogi, Singhal* and *Lapierre* 1980), and dopamine (DA) (*Horst* and *Spirit* 1974) in a number of brain areas, potentiates the stimulant effects of 5-OH-tryptophan and L-dopa following pargyline pretreatment (*Huidobro-Toro, Scotti de Corolis* and *Longo* 1974) and antagonizes the depressant effects of chlorpromazine (*Kruse* 1975) and barbiturates and ethanol (*Breese, Cott, Cooper, Prange, Lipton* and *Plotnikoff* 1975). In man, diagnostic doses of TRH have been reported to increase systolic blood pressure, diastolic blood pressure (*Borowski, Garofano, Rose* and *Levy* 1984), plasma prolactin (*Jacobs, Snyder* and *Utiger* 1973), NE (*Morley, Tuck* and *Mayes* 1981), and improve mood (reviewed by *Prange, Nemeroff* and *Loosen* 1979).

Despite the diversity of these effects, most studies of the effects of TRH in psychiatric illness have centered on the diagnostic utility of the TSH response to TRH. It is now well established that a smaller than normal ("blunted") TSH response occurs more frequently in depressives than in normals. Of 47 studies reviewed by *Loosen* and *Prange* in 1982, 41 found marked blunting in depressives. A number of authors have also reported that unipolar depressives have a more blunted TSH response than bipolar depressives (*Gold, Pottash, Ryan, Davies, Sweeney* and *Martin* 1979; 1980; *Linkowski, Bravman* and *Mendlewicz* 1981; *Kirstein, Gold, Eckstein, Martin* and *Pottash* 1982), but a number of negative reports have also appeared (e.g., *Amsterdam, Winokur, Mendels* and *Snyder* 1979).

The mood-elevating effects of TRH may also differ in various classes of depressives. For example, *Deniker, Ginestet, Loo, Zarifan* and *Cottereau* (1974) reported marked improvement in mood of some bipolars after TRH, but no change in the emotional status of unipolars. To our knowledge, the cardiovascular effects of TRH in depressives have never been examined.

In this study, we have compared the cardiovascular, catecholamine, mood and TSH responses among patients with several types of affective disorder.

Methods

The subjects for this study were 22 males with a mean (± SD) age of 36 + 8 who were diagnosed by research diagnostic criteria as having a history of either major (N = 8), minor (N = 6), or bipolar (N = 4) depression, or schizoaffective disorder (N = 4). These inpatients at the VA Medical Center gave written consent to this study, which was approved by the Human Subjects Committee. On the day of the experiment, each subject was seated in a quiet room and had a cannula inserted into an antecubital vein. Thirty minutes prior to

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infusion, each subject was asked to rate himself using the Profile of Mood Scales (POMS) (*McNair* and *Lorr* 1964) and the Activation-Inhibition Scale (AIS) (*Janowsky* and *Davis* 1973), and was observer-rated by the Hamilton Scale (*Hamilton* 1967). Subjects were infused over a one-minute period with 500 μg TRH. Blood samples were drawn at −30, −1, +15, +30, +60 and +90 minutes. Blood pressure and heart rate were also measured at these times and again at +5 and +10 minutes. POMS and AIS were readministered 30 minutes following infusion.

Seventeen subjects received both active and placebo infusions, which were performed double blind. TSH was assayed by radioimmunoassay (*Utiger* 1965). Catecholamines were determined by the radioenzymatic method of *Durrett* and *Ziegler* (1980). Statistical analysis was performed using student paired t test, ANOVA for mixed designs, and Tukey's post hoc test for unconfounded interactions.

Results

No significant baseline differences were observed between groups on any of the parameters examined. Also, no significant changes occurred during the preinfusion period in any of the parameters that were repeatedly monitored during this time.

TSH Response

TSH was significantly elevated in the affective disorder patients 30 minutes following infusion with TRH (10.5 ± 0.9 μU/ml). No significant differences ($P > .3$) in the magnitude of this elevation were found between any of the groups (bipolar depression, 10.6 ± 1.3; major depression, 10.9 ± 2.2; minor depression, 11.7 ± 1.3; schizoaffective, 7.8 ± 1.1 uU/ml).

Cardiovascular Response

In the entire group of patients, systolic blood pressure was maximally elevated above baseline by 6.8 ± 1.7 mm Hg ($P = .007$) and diastolic blood pressure by 5.5 ± 1.6 ($P = .0016$) 5 minutes following TRH infusion (Fig. 1). Heart rate was reduced by a maximum of 7.6 ± 1.3 beats/min ($P < .001$) 10 minutes after infusion of TRH. None of these cardiovascular parameters were significantly altered following placebo infusion.

The schizoaffectives had a prolonged increase in systolic and diastolic blood pressures, whereas minor depressives had a transient elevation at 5 minutes postinfusion. Bipolar depressives had no change in blood pressure. These differences did not reach statistical significance ($P = .09$ by ANOVA for diastolic blood pressure). Bipolar depressives tended to have an increase in heart rate following TRH whereas the other three groups showed a consistent reduction. Differences in the heart rate between groups also were not statistically significant ($P = .23$ ANOVA).

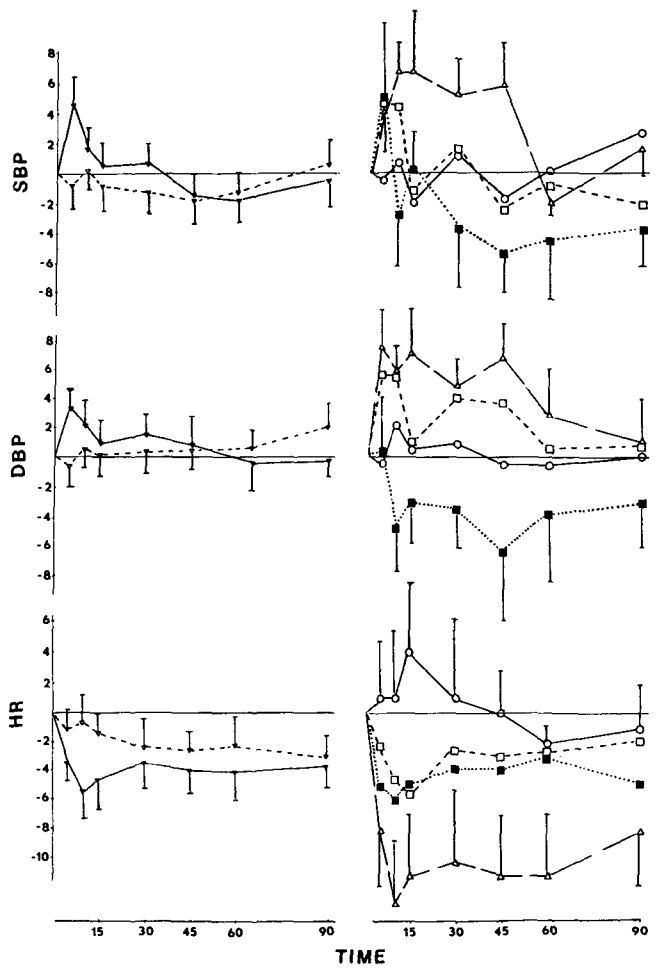

Fig. 1 The left panels show the change in systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR) for TRH (▼—▼) and placebo (▽—▽) infusions. The right panels show the same responses to TRH infusion in bipolar (o—o), schizoaffective (Δ—Δ), major depressive (□—□), and minor depressive (■—■) patients.

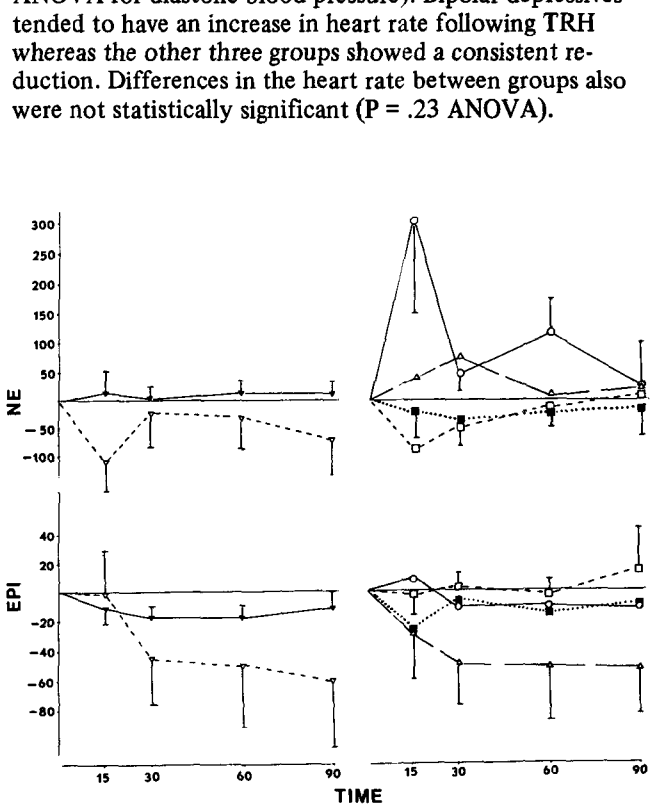

Fig. 2 The change in plasma levels of norepinephrine (NE) and epinephrine (EPI) in response to TRH and placebo (left panels) and in response to TRH in 4 groups of patients with affective disorders. Symbols as in Fig. 1.

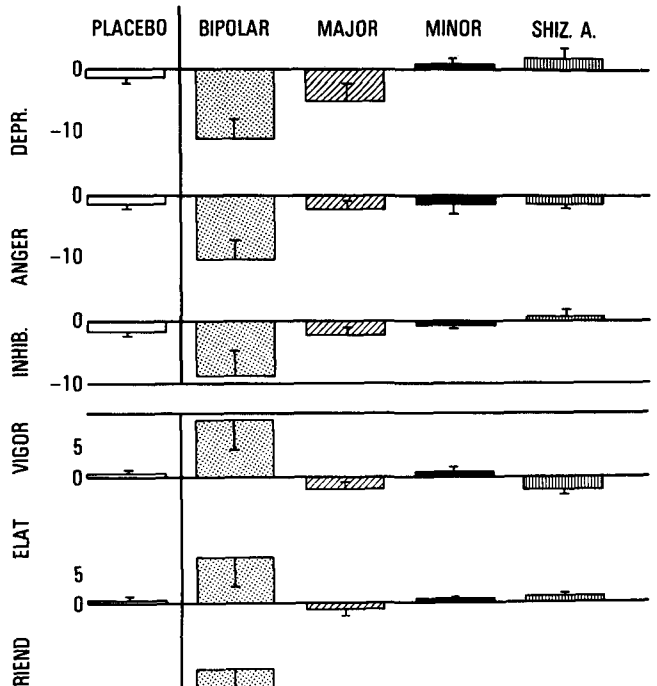

Fig. 3 Changes in ratings of friendliness (FRIEND), elation (ELAT), vigor (VIGOR), inhibition (INHIB), anger (ANGER), and depression (DEPR) in response to TRH infusion in patients with bipolar, major unipolar, or minor unipolar depression or schizoaffective disorder. The response of patients given a placebo infusion is shown in the left column.

Catecholamine Respone

Levels of NE after placebo were lower than after TRH (P = .02 for diagnosis x treatment x time interaction). The schizoaffective patients increased their NE after TRH (P < .05 response to TRH over time; Fig. 2). This effect was maximal 30 minutes following infusion. The log of plasma NE levels differed between treatment groups after TRH (P = .0023) because of the decrease in NE levels of the major depressive patients.

In contrast to NE levels, plasma E did not significantly change following TRH or differ between diagnostic groups. However, E levels were lower than NE, so assay variability comprised a larger fraction of E measurement.

Mood Response

In this group of psychiatric patients TRH significantly reduced the magnitude of several negative emotions, including anger (P = .006), tension (P = 0.0085), depression (P = .021), and inhibition (P = .032), while it increased friendliness (P = .021) (Fig. 3). In all of these instances except tension, there was a significant group X time interaction, indicating that these effects were attributable to changes occurring in bipolar depressives. Elation (P = .037) and vigor (P = .016) were also significantly increased in bipolar depressives, but not in any of the other groups.

Discussion

We found no differences in TSH response between any of the groups of affective disorder patients, in contrast to the differences in cardiovascular NE and mood responses to TRH. Bipolar depressives tended to diverge from the other groups in all three of these parameters. At 5 min post-infusion, they had no change in either systolic or diastolic blood pressure, whereas near maximal elevations were found in the other groups at this time. Only bipolar depressives tended to have an increase in heart rate following TRH and an increase in plasma NE at 15 min post-infusion. Since the tachycardia in bipolar depressives followed a time-course similar to their plasma NE elevation, this effect may be mediated by the sympathetic nervous system.

The sympathetic nervous system did not appear to mediate the pressor effects of TRH in these affective disorder patients. Schizoaffectives had a large and prolonged pressor response with a modest increase in plasma NE, whereas bipolar depressives showed no pressor response yet had a considerable increase in plasma NE. Studies of the effects of TRH (500 µg/i. v.) on plasma catecholamines in psychiatrically normal subjects are conflicting. *Morley, Tuck, Mayes, Rosenblatt* and *Hershman* (1981) reported that plasma NE is elevated to 170% of baseline levels following TRH, while *Zaloga, Chernow, Zajtchuk, Chin, Rainey* and *Lake* (1984) found no change. Although animal studies have consistently found marked catecholamine elevations following TRH, the doses employed are usually large (*Lux, Feuerstein* and *Faden* 1983) or given into the cerebral ventricles (*Brown* 1981), and several authors have provided evidence which indicates that these elevations are dissociated from the pressor effects of TRH (*Feuerstein, Zukowska-Grojec, Bayorh, Kopin* and *Faden* 1983; *Horita* and *Carino* 1977; *Lux, Feuerstein* and *Faden* 1983).

Of all the intergroup differences found, the most striking was the selective elevation of mood in bipolar depressives by TRH. This effect does not appear to be attributable to a generalized up-regulation of TRH receptors since the TSH response of bipolars was not different from the other affective disorder patients. An alternative hypothesis is that bipolars are exceptionally sensitive to antidepressant drugs in general. They are more responsive to lithium in acute depression than are unipolar depressives, and tricyclic anti-depressants induce mania more frequently in bipolars (*Gershon* 1978).

The TSH response to TRH is blunted in many depressives, but does not seem to differentiate between types of affective disorders. However, there are different trends for neuroendocrine and cardiovascular responses between groups of affective disorder patients. Both subjective and objective mood ratings differ in response to TRH between bipolar patients and those with other affective disorders. TRH elicits many responses other than an increase in TSH. Some of them are relatively easy to monitor and may be better measures of affective illness than the TSH response.

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