Short communication

# CARDIOVENTILATOR EFFECTS OF TRH IN ANAESTHETIZED RATS: ROLE OF THE BRAIN STEM

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Cardioventilator responses were studied in anaesthetized rats after injections of TRH into either the lateral (i.c.v. lat) or the fourth (i.c.v. IV) cerebral ventricles. TRH induced a more rapid hypertensive effect i.c.v. IV than i.c.v. lat. Blocking of the cerebral aqueduct abolished the hypertensive and tachypnoeic effects of TRH i.c.v. lat but not those of TRH i.c.v. IV. It is concluded that TRH increased blood pressure and ventilation rate via brain stem structures close to the fourth ventricle.

TRH    Cardiovascular    Ventilation    Brain stem

## 1. Introduction

Thyrotropin releasing hormone (TRH) exerts a variety of effects in addition to its endocrine action. Intracerebroventricular (i.c.v.) injections of TRH increase arterial pressure and heart rate in various species (Beale et al., 1977; Koivusalo et al., 1979; Eriksson and Gordin, 1981). A hypertensive effect of TRH is also seen in humans receiving the compound intravenously for diagnostic purposes (Borowski et al., 1984). Moreover, TRH i.c.v. stimulates the ventilation rate (Koivusalo et al., 1979; Hedner et al., 1983). Phylogenetic studies show that TRH is unable to stimulate thyroid function in certain amphibia and fish in spite of being abundantly present in the central nervous system. The finding that most of the TRH in the brain is found extrahypothalamically, that its binding sites are widely distributed in the CNS and that it is present in nerve terminals suggests that it would act as a neurotransmitter or neuromodulator (for review see Jackson, 1982).

Cardiovascular or ventilator responses have been elicited by local injections at various sites of the brain (e.g. Myers et al., 1977; Feuerstein et al., 1983). However, the central sites involved in the cardioventilator effects of TRH are not known precisely. Both endogenous TRH and its binding sites have been found in the region of the fourth ventricle (Eskay et al., 1983; Manaker et al., 1985). Accordingly, the present study was designed to find out to what extent the brain stem is involved in the cardioventilator effects of TRH.

## 2. Materials and methods

Male Wistar rats (240-300 g) were anaesthetized with urethane (1.5 g/kg i.p.). Ventilation rate (VR) and tidal volume (TV) were recorded by means of a hot wire flowmeter from the expiration of the spontaneously breathing rats. Mean arterial pressure (MAP) and heart rate (HR) were recorded from the femoral artery. TRH or solvent was injected stereotaxically into the fourth (i.c.v. IV) or into the lateral (i.c.v. lat) cerebral ventricle in a volume of 10 $\mu$l within 10-15 s. In some experiments the cerebral aqueduct was blocked by vertical insertion of a glass plate (0.1 mm thick and 3

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mm wide) at 7 mm caudally from the bregma, corresponding to the midcollicular level of the mesencephalon. The injection site was verified by staining with methylene blue. All the brains were examined histologically (HE staining) for determination of the exact level of the aqueduct block.

TRH (Sigma Chemical Co.) was dissolved in saline. In a pilot study a dose-dependent hypertensive, tachycardic and tachypnoeic response was observed at i.c.v. lat doses of 0.3-300 nmol/rat. A submaximal dose of 100 nmol/rat of TRH was used in the present study.

Unless stated otherwise, the results represent the maximal effects obtained within 15 min after each drug or treatment. Means ± S.E. are shown. Student's t-test for independent or dependent variables was used for statistical analysis.

## 3. Results

### 3.1. Time course of the effects of TRH

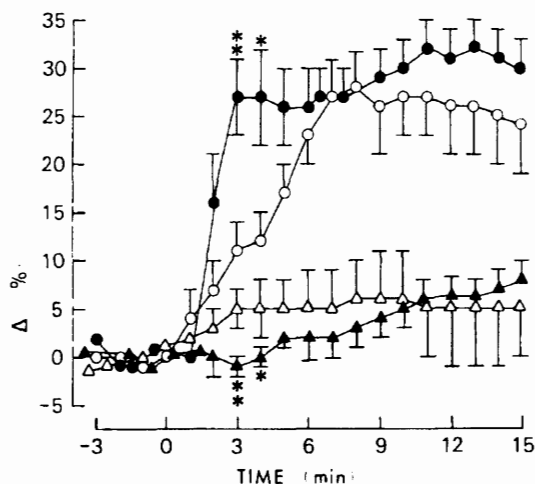TRH 100 nmol/rat i.c.v. IV or i.c.v. lat increased MAP and HR significantly and the max-



Fig. 1. Effects of TRH 100 nmol/rat given into the lateral (i.c.v. lat, open symbols, n = 7) or the fourth cerebral ventricle (i.c.v. IV, filled symbols, n = 6). Percentage changes in mean arterial pressure (MAP) are denoted as circles and those in heart rate (HR) as triangles. Statistical significance of the difference between i.c.v. IV and i.c.v. lat is indicated as follows: * P < 0.05, ** P < 0.01. Initial values in MAP (mm Hg) and HR (beats/min) respectively were: i.c.v. lat 103±7, 427±9; i.c.v. IV 95±7, 417±12.

imal effects were similar (fig. 1). However, TRH i.c.v. IV increased MAP by 27% within 3 min while 7 min elapsed till the corresponding effect was reached after i.c.v. lat. The difference in the response times was significant (P < 0.01). HR showed a 5% increase after TRH i.c.v. IV after 10 min while the same effect appeared within 3 min after TRH i.c.v. lat (P < 0.01).

The TRH-induced increase in VR was 39 ± 12% (P < 0.05, n = 6) after i.c.v. IV and 27 ± 4% (P < 0.01, n = 7) after i.c.v. lat. There were no significant differences between the groups in the changes in VR recorded during the 15 min observation time. TRH i.c.v. IV increased TV by 80 ± 17% (P < 0.05, n = 6) while only a negligible effect was seen (6 ± 4%, n = 7) after TRH i.c.v. lat. The differences between groups were significant at 5-15 min (P < 0.05-0.01).

### 3.2. Effect of blockade of the cerebral aqueduct on the responses to TRH

Blocking of the aqueduct did not cause significant changes in MAP or VR (3 ± 6 mm Hg and −8 ± 6 breaths/min respectively). However, HR and TV were set on a significantly higher level for the entire duration of the experiment. The increase in HR was 43 ± 11 beats/min (P < 0.001) and that in TV 27 ± 7% (P < 0.05).

In non-blocked rats TRH i.c.v. lat increased MAP significantly (fig. 2a) while only a negligible effect was seen in the presence of the block. However, in the presence of the block, TRH i.c.v. IV still exerted a strong hypertensive effect. In non-blocked rats TRH i.c.v. lat induced a tachycardiac response while the heart rate increases after TRH i.c.v. lat or i.c.v. IV were not significant in presence of the block.

In non-blocked rats TRH i.c.v. lat significantly increased VR while this effect was completely abolished after blocking of the aqueduct (fig. 2b). However, in the presence of the block TRH i.c.v. IV still induced a clear tachypnoeic response. In the absence of the block TRH i.c.v. lat caused only negligible effects on TV. In the presence of the block neither TRH i.c.v. lat nor TRH i.c.v. IV exerted any significant effects on TV.
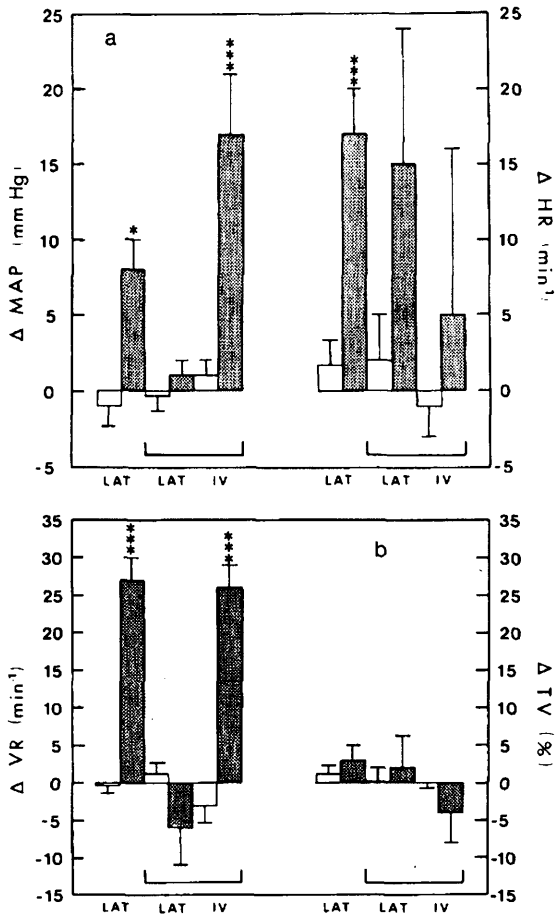
Fig. 2. (a) Maximal effects of TRH 100 nmol/rat given either into the lateral (LAT) or the fourth cerebral ventricle (IV). Filled bars: TRH treatment (n = 6); open bars: solvent (n = 6). The group of bars on the left shows the changes in mean arterial pressure (MAP) and that on the right shows the changes in heart rate (HR). The line under the rightmost four bars in each group (————) represents effects in the presence of the block of the cerebral aqueduct. Statistical significance vs. solvent is denoted as follows: * P < 0.05, *** P < 0.001. Initial values in MAP (mm Hg) and HR (beats/min) respectively were: LAT 112±9, 452±5; LAT with block 122±18, 510±17; IV with block 116±14, 525±20. These values did not differ statistically from those for the group treated with solvent. (b) Maximal effects of TRH 100 nmol/rat given into the lateral (LAT) or the fourth cerebral ventricle (IV). Filled bars: TRH treatment (n = 6); open bars: solvent (n = 6). The group of bars on the left shows the changes in ventilation rate (VR) and that on the right shows the changes in ventilation tidal volume (TV). The line under the rightmost four bars in each group (————) represents effects in the presence of the block of the cerebral aqueduct. Statistical significance vs. solvent is denoted as follows: *** P < 0.001. Initial values in VR (breaths/min) were: LAT 93±5, LAT with block 130±6, IV with block 98±3. These values did not differ statistically from those for the group treated with solvent. The percentage changes in TV were calculated from arbitrary units.

## 4. Discussion

TRH given in the fourth cerebral ventricle induced a more rapid increase in blood pressure than TRH given in the lateral ventricle. Moreover, TRH still exerted a strong hypertensive effect in the fourth ventricle when its access to the third and lateral ventricles was hindered by the aqueduct block. These findings indicate that at least a part of the hypertensive effect of TRH was mediated via brain stem structures close to the fourth ventricle. It is consistent with the present results that an almost instant pressor response (20 s) was seen after intracisternal injection of TRH in rabbits (Beale et al., 1977). The fact that the aqueduct block abolished the hypertensive effect of TRH in the lateral ventricle does not exclude other sites of action e.g. the hypothalamus or the preoptic area as suggested by others (Feuerstein et al., 1983). It is possible that the partial transection of the mesencephalon damaged those descending pathways necessary for the expression of the hypertensive effect of TRH in the diencephalic sites.

TRH induced a more rapid tachycardiac response when given in the lateral than when given in the fourth ventricle, suggesting a site of action rostral to the fourth ventricle. This notion also conforms with the finding that in blocked rats TRH did not induce any significant tachycardia when given in the fourth ventricle. However, no conclusive evidence could be obtained because of the failure of TRH to induce significant tachycardia from the lateral ventricle after blocking of the aqueduct. A possible explanation for the lack of effect could be the partial transection and the initially higher heart rate level due to the block. In accordance with a previous report (Sirén and Paakkari, 1984) the results suggest that the hypertensive and tachycardiac effects of TRH were not mediated via identical mechanisms.

The region of the fourth ventricle was involved in the tachypnoeic effect of TRH since a strong increase in ventilation rate was induced by TRH given in the fourth ventricle in spite of the aqueduct block. Also Hedner et al. (1983) found that the stimulation of the ventilation rate by TRH was strongest when the compound was administered into the fourth ventricle.

In accordance with earlier reports (e.g.

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Koivusalo et al., 1979; Hedner et al., 1983) no increase in ventilation tidal volume was seen after the injection of TRH into the lateral ventricle. However, in the present study a clear increase in tidal volume was observed when the compound was injected into the fourth ventricle in non-blocked animals but not in those with the block. The absence of the effect in the latter group may have been due to the increased basal tidal volume caused by the block. An alternative explanation could be that the block in the mesencephalic level ablated the area sensitive to this particular effect of TRH. Myers et al. (1977) reported an increase in ventilation rate after local mesencephalic injections of TRH. However, no data on the possible changes in tidal volume were presented.

The present findings suggest that TRH may be involved in cardioventilator regulation in the brain stem regions close to the fourth cerebral ventricle.

## Acknowledgements

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