Simultaneous Administration of TRH and Sulpiride Caused Additive but Not Synergistic PRL Responses in Normal Subjects

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Abstract. In order to study the mode of action of TRH and sulpiride in man, we administered TRH (500 μg, iv) and sulpiride (DA D2 receptor antagonist, 100 mg, im) simultaneously to 6 normal females (20–21 yr). Normal females showed significantly greater PRL increments and AUC in response to the combined administration compared to a single administration of each agent (P<0.05-0.01), while the increment and AUC in response to the combination did not exceed the sum of those responses to a single administration. In contrast, the combined administration of TRH and sulpiride did not elicit an enhanced response of plasma TSH. These results indicate that the sites of action of TRH and sulpiride might be different from each other, and these agents work additively with no interaction in human lactotrophs.

Key words: TRH, Sulpiride, PRL, TSH, Normal females.

RECENTLY, we have suggested that there are TRH-related and dopamine-related pituitary TSH and PRL-pools in patients with prolactinoma and normal female subjects, and also suggested that TRH and sulpiride (DA D2 receptor antagonist) modulate these hormone pools through a different intracellular transduction mechanism [1].

In rat and human thyrotrophs and lactotrophs, the mode of action of TRH and sulpiride might be different, i.e. TRH has been thought to act on the phosphatidylinositol-protein kinase C system and sulpiride to act on the adenylate-cyclase-protein kinase A system by suppressing the inhibitory GTP binding protein (Gi) which is stimulated by dopamine (DA) [2–8]. The fact that simultaneous administration of TRH and sulpiride caused an additive TSH and PRL response in prolactinoma patients, as was shown in a previous report [1], seems to support the above explanations.

To study whether such enhanced responses occur even in normal subjects or not, plasma PRL and TSH responses to simultaneous administration of TRH and sulpiride were examined in these subjects. Our results suggest that TRH and sulpiride modulate PRL secretion through different intracellular transduction mechanisms as mentioned above.

Materials and Methods

Six normal females in an early follicular phase (20–21 yr) were studied. Informed consent was obtained from every normal subject. After an overnight fast, these subjects were given a single administration of TRH (500 μg, iv) or sulpiride (100 mg, im), or a simultaneous administration of these agents. These studies were performed with an interval of 7 days or more, and blood specimens
were collected at -30 min, immediately before (0 min), and 15, 30, 45, 60, 90 and 120 min after the administration of the agent(s).

Plasma PRL and TSH were measured with an immunoradiometric assay kit (Daiichi, Tokyo) and an ultrasensitive immunofluorometric assay kit (Pharmacia, Uppsala), respectively. All samples from an individual subject were analysed in duplicate in the same assay, and the area under the response curve (AUC) over the baseline was calculated by a trapezoidal integration. The intra- and interassay coefficients of variance were 3.2 and 5.6% for PRL, 4.0 and 5.2% for TSH, and the sensitivities of the PRL and TSH assays were 0.3 μg/l and 0.02 mU/l, respectively [1]. Analysis of variance followed by Student/Newmann-Keuls test was used for statistical analyses, and data are shown as the mean ± SEM.

Fig. 1. Plasma PRL responses to a single administration of TRH (●—●) and sulpiride (○—○) or the combined administration of these agents (△—△) in 6 normal female subjects (left panel). The area under the response curve over the baseline (AUC) is shown in the right panel. vs. combined administration: *, P<0.05; **, P<0.01.

Fig. 2. Plasma TSH responses to a single administration of TRH (●—●) and sulpiride (○—○) or the combined administration (△—△) in 6 normal female subjects (left panel). The AUC is shown in the right panel. vs. combined administration: *, P<0.01.
**Results**

*Plasma PRL and TSH responses to single or combined administration of TRH and sulpiride in 6 normal females*

Plasma PRL response to the combined administration of TRH and sulpiride in 6 normal females (max. ∆PRL, 171.4±25.8; AUC, 12214.4±1277.2) significantly exceeded the response to a single administration of TRH (max. ∆PRL, 41.0±8.1, P<0.01; AUC, 2508.5±637.5, P<0.01) and sulpiride (max. ∆PRL, 92.9±11.8, P<0.05; AUC, 8348.2±957.7, P<0.05), but did not exceed the sum of the response of TRH and sulpiride (max. ∆PRL, 133.9±20.6 ƒÊg/l, P=NS; AUC, 10856.7±1518.6 ƒÊg/lxmin, P=NS) (Fig. 1).

In contrast, plasma TSH response to the combined administration of TRH and sulpiride (max. ∆TSH, 13.6±2.7; AUC, 991.3±167.7) was not different from the response to a single administration of TRH (max. ∆TSH, 19.0±5.4 mU/l; AUC, 1168.9±243.0 mU/lxmin) (Fig. 2). Normal females showed a slight TSH increase due to sulpiride, but it did not reach statistical significance compared to the basal value. The mean basal PRL and TSH values at 3 examinations were not significantly different (data not shown).

**Discussion**

In this study, normal female subjects showed an additive PRL response to the simultaneous administration of TRH and sulpiride, but no such response was observed in TSH. The enhanced response due to TRH and sulpiride indicates that the sites of action of these agents are different, since the doses of TRH and sulpiride are considered to be maximal [1, 9, 10].

In *in vitro* studies on rat and human pituitary cells, TRH stimulates TSH and PRL secretion through the phosphatidylinositol system [2–7], while DA mainly inhibits TSH and PRL secretion by stimulating the inhibitory GTP binding protein (Gi) and inhibiting the subsequent cAMP-protein kinase A system [2, 4, 7, 8]. The DA antagonist therefore stimulates the cAMP-protein kinase A system by inhibiting the DA action, although we must consider the possibility that DA can also act on a number of other transduction mechanisms such as IP3 and arachidonic acid generation, and intracellular calcium concentrations [11–14].

Regarding the pituitary cells, it is reported that simultaneous stimulation of different second messenger systems synergistically enhances the hormone secretion (so-called cross talking) [15–21]. However, simultaneous administration of TRH and DA antagonist in our study did not result in any synergism in PRL or TSH response in normal females, only enhanced responses compared to the single administration of these agents.

It is conceivable that TRH and sulpiride stimulate PRL secretion through different intracellular mechanisms without having distinct interactions. This is inconsistent with the fact that DA withdrawal (causing inactivation of Gi and resultant activation of the adenylate cyclase-protein kinase A system) in estrogen treated rats is known to synergistically potentiate the PRL-releasing action of TRH [20]. The reason for such a discrepancy between man and rat is not yet clear.

In this study, the simultaneous administration of TRH and sulpiride did not cause enhanced TSH response, which was quite different from prolactinoma patients. This may mean that hypothalamic DA tone is lower in normal subjects than in prolactinoma patients, and DA-related TSH pools in their thyrotrophs and the response to sulpiride are subtle [1, 22].

Sulpiride does not increase TSH secretion in hypothalamic disorders with hyperprolactinemia, and it can differentiate prolactinoma from those disorders [23]. Further, as the combined administration of sulpiride and TRH causes clearer TSH increments probably only in prolactinoma patients, such an aberrant TSH response to sulpiride alone and to the combined administration of sulpiride and TRH would be a very useful indicator for the differential diagnosis of hyperprolactinemia [1].

In conclusion, the intracellular transduction mechanisms of TRH and sulpiride might be different from each other, and these agents work additively but not synergistically in human lactotrophs.

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References


