Studies on Facial Temperature Rise and Involvement of Serotonin in the Respiratory Stimulation by CRH

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Summary

Following an intravenous injection of 100 ug hCRH a facial flushing can frequently be observed along with respiratory stimulation. Both effects can be mediated by a common transmitter. Serotonin is well known to produce facial flush as well as to modulate respiration. In order to clarify if serotonin is a common mediator for facial flush and respiratory stimulation after i. v. application of hCRH, we studied the time course of facial skin temperatures and respiratory stimulation after intravenous injection of 100 ug hCRH in 10 healthy subjects. Furthermore, we measured respiratory stimulation after i. v. administration of 100 ug hCRH in 10 healthy subjects pretreated with the serotonin antagonist cyproheptadine. Facial skin temperatures reached maximum levels 9 min after CRH administration and remained raised for more than 60 min. Respiratory stimulation occurred within the first minute after CRH administration and reached a maximum during the second minute, but could no longer be observed after 10 min. Serum serotonin levels did not change after CRH stimulation (in doses up to 3 ug/kg body weight), and cyproheptadine did not abolish the respiratory stimulation effect of hCRH in a dosage sufficient to suppess CRH.-induced cortisol secretion.

We thus conclude, that facial flushing and respiratory stimulation after intravenous administration of hCRH are not mediated through serotonin.

Key words

Facial Skin Temperature – Serotonin – CRH

Introduction

CRH has been shown to be a major regulator of the hypothalamic-pituitary-adrenal axis (*Vale, Spiess, Rivier* and *Rivier* 1981; *Vale, Rivier, Brown, Spiess, Koob, Swanson, Bilezikjian, Bloom* and *Rivier* 1983). However, the biological action of CRH is not restricted to the endocrine stimulation of the pituitary adrenal axis. Several other functions of CRH have been observed. CRH stimulates the autonomic nervous system (*Brown* and *Fisher* 1985; *Fisher, Rivier, Rivier, Spiess* and *Vale* 1982), prevents weight gain (*Rohner-Jeanrenaud, Walker, Greco-Perotto* and *Jeanrenaud* 1989; *McLaughlin, Stern* and *Baile* 1987), influences behaviour (*Britton, Koob, Rivier* and *Vale* 1982), produces facial flush (*Orth, Jackson, DeCherney, DeBold, Alexander, Island, Rivier, Rivier, Spiess* and *Vale* 1983), stimulates respiration in man (*Oppermann, Nink, Huber, Krause* and *Schulz* 1986) and in experimental animals (*Böhmer, Schmid, Oppermann* and *Ramsbott* 1985). This latter effect is not mediated by ACTH or cortisol as we were able to demonstrate in a recent study (*Huber, Krause, Nink, Lehnert* and *Beyer* 1989) and was verified by *Butzmann, Rühmann, Wagner, Fabel* and *von zur Mühlen* (1990). The mechanism by which CRH causes these effects is not yet fully understood. It is probable that the effect on respiration is not only a pharmacological but a physiological one, since *Böhmer* et al. could block the ventilatory CRH-response in the rabbit by application of an alpha-helical CRH-antagonist (*Böhmer, Schmid* and *Ramsbott* 1990). Because of ethical reasons this CRH-antagonist can not be applied in human studies. CRH might exert its effects directly or mediated through a common or different mediators.

The aim of our present study was to find out whether or not serotonin might be a common mediator for flush and respiratory stimulation.

The role of serotonin as a flush-producing substance has not been unequivocally accepted (*Grahame-Smith* 1987). However, there is some evidence that serotonin can act as a vasodilatator (*Furchgott* 1983; *Haddy, Gordon* and *Emanuel* 1959; *Humphrey* 1984). Neuroanatomical studies have also shown the existence of serotonin in structures classically associated with breathing regulation, such as n. paraventricularis dorsalis et ventralis, n. ambiguus, n. ractus solitarius (*Palkovits, Brownstein* and *Saavedra* 1974). Furthermore, serotonin has been shown to stimulate respiratory motor output in experimental animals after i. c. v. administration (*Millhorn, Eldridge, Waldrop* and *Klingler* 1983; *Millhorn, Eldridge* and *Waldrop* 1980); although other studies reported contradictory results (*Lundberg, Mueller* and *Breese* 1980; *Armijo, Mediavilla* and *Florez* 1979). Furthermore, serotonin is involved in the activation of the hypothalamic-pituitary-adrenal axis (*Holmes, Di Renzo, Beckford, Gillham* and *Jones* 1982; *Plonk* and *Feldman* 1976; *Lewis* and *Sherman* 1984). At the hypothalamic level, it is able to stimulate CRH secretion (*Nakagami, Suda, Yajima, Ushiyama, Tomori, Sumitomo, Demura* and *Shizume* 1986; *Buckingham* and *Hodges* 1979), and on the pituitary level it facilitates the action of CRH on ACTH secretion. Cyproheptadine has antiserotonergic prop-

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erties with high affinity to 5-HT_2 binding sites (*Bradley, Engel, Feniuk, Fozard, Humphrey, Middlemiss, Mylecharane, Richardson* and *Saxena* 1986).

Besides this, only an antihistaminergic effect is noteworthy in therapeutical doses. Serotonin stimulates the endogenous CRH secretion at the hypothalamic level, which can be suppressed by various serotoninantagonists, e. g. cyproheptadine (*Holmes* et al. 1982; *Nakagami* et al. 1986; *Buckingham* and *Hodges* 1979). Incubation of cultured corticotroph adenoma cells with cyproheptadine shows a significant decrease of ACTH release, which can be blocked by the addition of equimolar serotonin (*Ishibashi* and *Yamaji* 1981). Meanwhile it has been shown that $5HT_{1A}$-receptors are involved in ACTH secretion (*Lesch, Söhnle, Poten, Rupprecht* and *Schulte* 1990). Further study is necessary to determine whether other types of 5HT-receptors mediate the ACTH release. Cyproheptadine also antagonizes ACTH and cortisol release after i. v. administration of CRH in healthy volunteers (*Winkelmann, Allolio, Deuss* and *Schulte* 1987). Therefore, it is evident that cyproheptadine must affect serotonergic mechanisms below the hypothalamic level as well. A corresponding model can possibly be assumed for the change of ventilatory parameters after CRH administration. The aim of our present study was to elucidate the role of serotonin as a possible mediator of respiratory stimulation by CRH.

Subjects and Methods

All our human studies with CRH had been approved by the local ethical committee. For technical reasons it was impossible to measure facial flush and respiration parameters in the same experiment. We therefore studied our probands on two different occasions.

a. flush

10 healthy volunteers, 4 females, 6 males, aged 23 to 32 (mean 25.6 ± 3 years) were injected with 100 ug hCRH (Bachem) intravenously after a minimum of 30 min rest in the supine position. A thermographic camera (TV-Probeye 4000, Atomika, Munich, Germany) was used to measure facial skin temperatures at various points. Thermographic pictures were recorded continuously and evaluations were made at distinct time points. Additionally, 6 of the volunteers received the solvent as a placebo (1 ml 0.15 mol/l NaCl with 0.02% HCl, pH = 2.75) on a second occasion.

b. cyproheptadine

We studied 10 healthy male volunteers, mean age 24.6 ± 1.6 years, mean height 180.1 ± 5.6 cm, mean bodywieght 76.3 ± 9.1 kg. None of them were having any drug therapy and none had a history of respiratory disease. After being informed of the purpose, nature and possible hazards of the experimental protocol, each subject gave his written consent. All measurements were conducted with the subjects in a semirecumbent position. They were instructed to close their eyes for better relaxation. A butterfly needle was inserted in a forearm vein and kept patent by a slow infusion of 0.150 mol/l NaCl solution. The test persons wore nose clamps and were connected to a pneumotachograph (A. Fleisch, Switzerland) by rubber mouth pieces to determine the respiratory frequency, tidal volume, and minute volume. End-tidal pO_2 and pCO_2 were measured by mass-spectrometry (Perkin-Elmer 1100, Medical gas Analyzer). In order to avoid influences of blood-sampling on respiratory parameters during the first relevant minutes after CRH-injection, blood for determination of plasma-ACTH and cortisol was collected 30 and 15 min before, then 30 min after CRH administration. Plasma cortisol and ACTH were determined in duplicate using specific RIAs purchased from Serono (Freiburg, Germany) and from IBL (Hamburg, Germany) respectively. Cyproheptadine-HCl was supplied by Merck, Rahway, N. J., USA.

The tests were performed on two different occassions (i. e. with and without cyproheptadine; on days without cyproheptadine the subjects received the solvent), so that each subject also functioned as a control. 24 min before CRH injection the cyproheptadine infusion was started and continued on the average for 30 min. Each subject received 2.5 ug/kg body weight/min. This dosage had been shown earlier to suppress CRH stimulated cortisol release (*Winkelmann* et al. 1987). 100 ug hCRH (Bissendorf-Peptide, Wedemark 2, Germany) dissolved in 2 ml 0.15 mol/NaCl with 0.01% HCl were administered i. v. via the infusion line over a period of 30 sec. The respiratory parameters were measured continuously for at least 10 min before and 20 min after CRH administration. In a separate study it had been assured that the solvent for CRH had no effect on respiratory parameters (data not shown). The study was performed single blind, i. e. the subjects did not know what was being injected. Furthermore, the evaluation of the recordings was performed in the same fashion.

Statistical analysis

Changes in facial skin temperatures were evaluated using analysis of variance. For statistical evaluation of ventilatory parameters in the cyproheptadine study, the time intervals of 6 min before and 6 min after the CRH injection were considered. To test the influence of cyproheptadine paired differences of the mean values with and without cyproheptadine were summed for each subject. To test the effect of CRH on respiration and cortisol secretion paired differences of values before and after CRH administration were considered. To test the influence of cyproheptadine on steady-state parameters, the differences between the values with and without cyproheptadine each before CRH injection were calculated. Significance was tested using Wilcoxon statistics for paired variables. p-values < 0.05 were considered significant. If not otherwise stated mean values $\pm$ D are given throughout.

Results

After CRH administration, facial skin temperatures rose sharply within the first minute in all subjects. Maxima were reached 9 min after the beginning of CRH administration. Thereafter, temperatures decreased slightly but were still above the starting temperatures after 60 min. The rise was most pronounced in the region of both cheeks (Figure 1). Administration of the solvent alone provoked no rise in temperature.

Mean cortisol starting values, without cyproheptadine 15 min before CRH administration, were significantly stimulated by 100 ug hCRH i. v. ($p < 0.01$). Cyproheptadine had no effect on the basal values of cortisol, but caused a complete suppression of CRH induced cortisol release in 6 of 10 subjects (further referred to as responders), while in the others an attenuated increase could be observed (Table 1).

Minute volumes rose from 6.7 ± 1.1 to 9.9 ± 2.2 l/min ($p < 0.01$) without cyproheptadine and from 7.1 ± 0.8 to 10.7 ± 2.3 l/min ($p < 0.01$) after pretreatment with cyproheptadine, providing evidence that cyproheptadine exerted no significant effects on basal values or on the CRH induced increase of minute volume (Figure 2).

Tidal volumes rose from 0.51 ± 0.09 l without cyproheptadine (0.52 ± 0.08 l with cyproheptadine) to

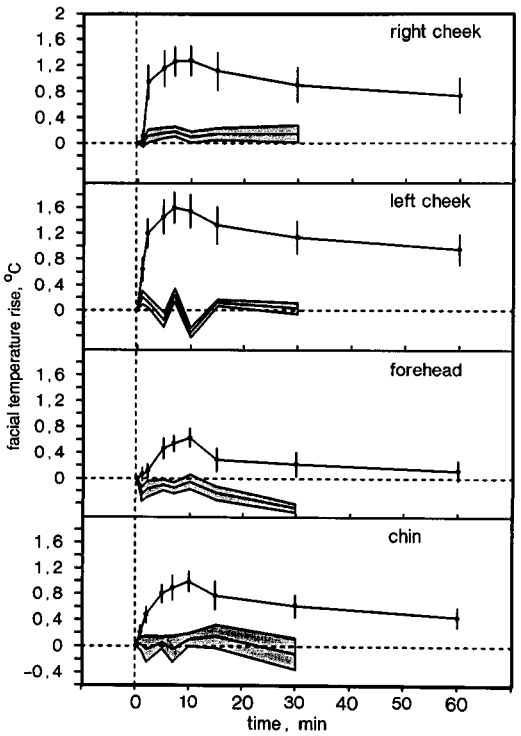

Fig. 1 Time course of facial skin temperature rise at different regions after intravenous administration of 100 ug hCRH to 10 healthy volunteers; shaded areas represent results after application of solvent alone; deviations are SEM.

0.69 ± 0.12 l (0.69 ± 0.13 l with cyproheptadine), ($p < 0.01$ for both, influence of cyproheptadine n. s., Figure 2).

End-tidal pO_2 increased from 100.3 ± 3.0 mmHg (100.2 ± 4.6 with cyproheptadine) to 112.2 ± 4.2 mmHg (112.6 ± 6.0 with cyproheptadine), ($p < 0.01$ for both, Figure 3, influence of cyproheptadine n. s.).

PCO_2-values decreased from 40.9 ± 2.6 mmHg (40.5 ± 2.8 with cyproheptadine) to 35.8 ± 3.3 mmHg (34.9 ± 3.4 with cyproheptadine), ($p < 0.01$ for both, Figure 3, influence of cyproheptadine n. s.).

Breathing frequency did not significantly change either with or without cyproheptadine after CRH administration.

Cyproheptadine did not exert any significant effects on the ventilatory parameters either on the steady-state values or on the CRH induced change of breathing parameters. Ventilatory parameters did not differ between responders and non-responders.

Facial flushing was observed in 9 out of 10 volunteers without and in all volunteers with cyproheptadine pretreatment, whilst respiratory stimulation could be seen in all of them.

Most of the subjects experienced symptoms of tiredness, numbness, dizziness and mouth dryness after the intravenous administration of cyproheptadine.

Table 1 Cortisol (nmol/l) and ACTH (pg/ml) before and after CRH stimulation with and without cyproheptadine; results from responders are given in parentheses.

	−15'	+30'	p
	without cyproheptadine		
Cortisol	261.1 ± 114.3	479 ± 84	< 0.01
ug/dl	(279 ± 118)	(404 ± 118)	< 0.01
ACTH	24 ± 15	32 ± 20	> 0.05
pg/ml	(29 ± 16)	(38 ± 22)	> 0.05
	with cyproheptadine		
Cortisol	285.9 ± 165.6	347 ± 220	> 0.05
ug/dl	(229.1 ± 87.3)	(237.9 ± 80.3)	> 0.05
ACTH	21.6 ± 9.4	33.9 ± 25	> 0.05
pg/ml	(23.7 ± 9.7)	(23.5 ± 9.1)	> 0.05

Discussion

All volunteers in this study responded to an intravenous administration of CRH with an elevation of facial skin temperature. *Schürmeyer* et al. (*Schürmeyer, Avgerinos, Gold, Galluci, Tomai, Cutler, Loriaux* and *Chrousos* 1984) described a marked flush after CRH administration in only 30% of his volunteers. However, the ability to observe a facial flushing depends on the individual's type of skin (e. g. colouring and thickness). Thus, for the study of facial flushing the thermographic measurement of skin temperatures is a more objective tool. Our data show that the time courses of facial skin temperature and respiratory stimulation after intravenous CRH are quite different. Facial skin temperatures reached maximal values after 10 min when a respiratory stimulation can no longer be observed, and remained elevated for more than 60 min. The different kinetics of both actions may not entirely exclude serotonin as a common transmitter. Following serotonin administration vasodilatation is mediated through 5-HT_1 receptors, to which serotonin has a high affinity, rather than through 5-HT_2 receptors (*Peroutka* 1984). Thus, lower serotonin concentrations than those required for the release of $5HT_2$-mediated effects such as respiratory control might be sufficient to release 5-HT_1 mediated effects such as vasodilatation. However, the mechanism of changing ventilatory parameters is not yet completely clear (see below).

In a separate trial we studied the effects of i. v. CRH (in doses up to 3 ug/kg body weight of healthy volunteers) on plasma serotonin levels. A significant change could not be observed after 5, 10, 15 and up to 120 minutes (data not shown).

However, this does not exclude the possibility that central serotonin levels are influenced by CRH injection. Serotonin has been reported to modulate respiration. Several studies found contradictory effects of serotonin, e. g. depression of respiration (*Millhorn* et al. 1983; *Lundberg, Mueller* and *Breese* 1980; *Armijo, Mediavilla* and *Florez* 1979) and stimulation of ventilatory parameters (*Millhorn* et al. 1983; *Millhorn, Eldridge* and *Waldrop* 1980). This observation of different effects of serotonin depends on the type and site of application (*Millhorn* et al. 1983). Furthermore, it is not quite clear which

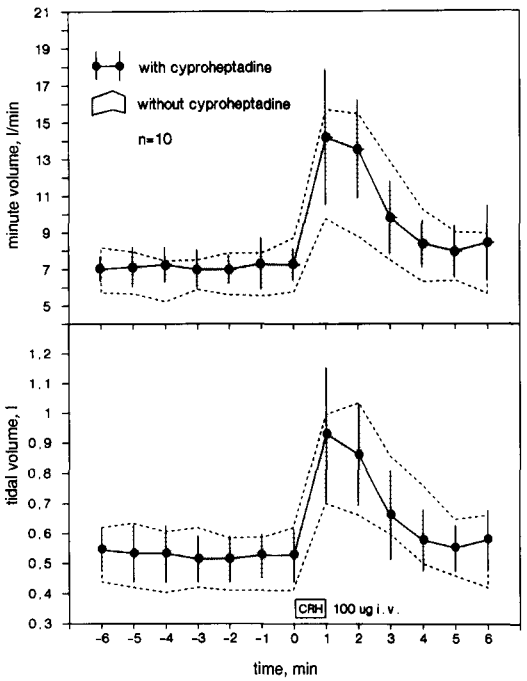

Fig. 2 Effect of cyproheptadine on tidal volume (lower panel) and minute volume (upper panel) before and after intravenous administration of 100 ug hCRH to 10 healthy volunteers. The shaded areas show the respective ranges without cyproheptadine.

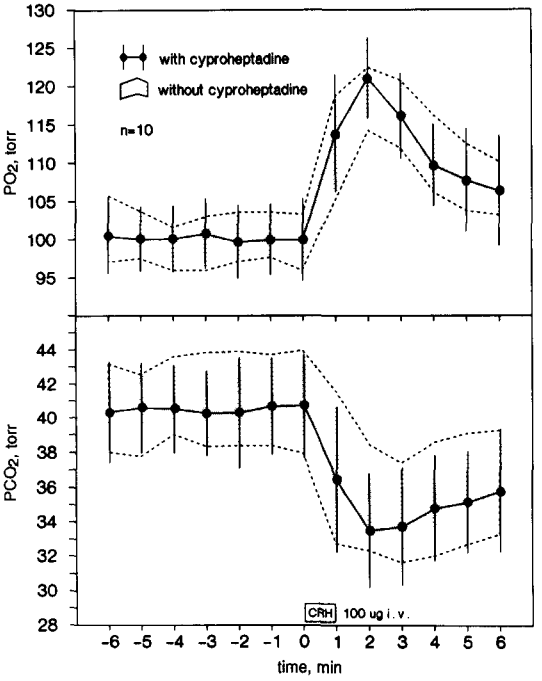

Fig. 3 Effect of cyproheptadine on basal and CRH-stimulated end-tidal O_2 (upper panel) and end-tidal CO_2 (lower panel) partial pressures in 10 healthy volunteers. Shaded areas represent ranges without cyproheptadine.

type of 5-HT-receptor is involved in ventilatory regulation. Stimulation of 5-HT_1A-receptors results in an increase in respiratory rate rather than in an augmented tidal volume, as found by *Gillis, Hill, Kirby, Quest, Hamosh, Norman* and *Kellar* (1989). Our experiments show an increase of minute volume after CRH administration via an increase of tidal volume while the respiratory rate remains uninfluenced. 5-HT_2 receptors are involved in the regulation of several autonomic functions such as thermoregulation and cardiovascular control. The effects of this receptor type differ from those of 5-HT_1A mediated effects (*Gillis* et al. 1989; *Gudelsky, Koenig* and *Meltzer* 1986). If serotonin really is involved in respiratory stimulation after CRH-application, it seems likely that 5-HT_2-receptors are also involved in mechanisms of respiratory control.

Most of our volunteers experienced central side effects after the intravenous administration of cyproheptadine, indicating that the applied dose of cyproheptadine was sufficient to exert antiserotonergic and antihistaminergic actions in the CNS. This assumption is further underlined by our observation that in 6 of 10 volunteers the CRH-stimulated cortisol rise was completely suppressed and in 4 of 10 partially as compared intraindividually to the tests conducted without cyproheptadine. Application of higher doses of cyproheptadine would have brought about more serious side effects without improving results. These results are in accordance with studies on cultured pituitary adenoma cells, which showed a decrease of ACTH secretion after incubation with cyproheptadine (*Ishibashi* and *Yamaji* 1981). Studies on patients with Nelson's syndrome (*Hirata, Nakashima, Uchihashi, Tomita, Fujita* and *Ikeda* 1984) and Cushing's disease (*Krieger, Amorosa* and *Linick* 1975) and studies on healthy volunteers after CRH application (*Winkelmann* et al. 1987) have shown an ACTH- and cortisol depressing effect of this substance. In contrast, *Brademann, Schürmeyer* and *von zur Mühlen* (1989) did not find any ACTH suppressive effect of cyproheptadine. These differences may be due to the use of lower cyproheptadine dosage given orally by these investigators. Since the respiratory response to CRH was unaltered in our volunteers it appears clear that the respiratory effect of CRH is not mediated by ACTH or cortisol. This finding is in concordance with our earlier observations, that dexamethasone does not influence the respiratory effect of CRH (*Huber* et al. 1989; *Butzmann* et al. 1990). In the applied dose cyproheptadine did not affect steady-state respiratory parameters or basal cortisol levels.

Intravenous injection of 100 ug CRH caused facial flushing in 9 of 10 subjects regardless whether or not they had been pretreated with cyproheptadine. This observation can be explained by the low affinity of cyproheptadine for 5HT_1 receptors mediating vasodilatation. Furthermore, since cyproheptadine also has antihistaminergic properties it is most likely that histamine is not the mediator of either flush or respiratory stimulation after i. v. CRH.

In conclusion, our results do not provide sufficient evidence for serotonin as a common mediator for facial flushing and respiratory stimulation. From the time course of the respiratory stimulation effect it is likely that CRH stimulates respiration directly rather than through a mediator.

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