

GABAergic Control of Anterior Pituitary Function in Humans

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INTRODUCTION

It is now generally accepted that γ -aminobutyric acid (GABA) acts as an inhibitory neurotransmitter (5,30,82,90). In mammals, high concentrations of GABA are found in brain and spinal cord, but only trace amounts are present in peripheral tissues (82,90). Pharmacological studies have demonstrated that GABA may modulate the function of other central neurotransmitters. For instance, GABA seems to exert a dual control over dopaminergic (36,101) and noradrenergic (9) function, being able either to stimulate or to inhibit dopamine (DA) and noradrenaline (NA) release (9,36). Moreover, GABA has been reported to exert a tonic inhibitory control over serotonergic neurons (33) and cholinergic cells (88). The existence of a functional interaction between GABA and endogenous opioid peptides has been also proposed (6). Since all these neurotransmitters and neuromodulators have been identified at hypothalamic level (10), it has been assumed that GABA might be involved in the regulation of hypothalamic-pituitary function.

This hypothesis has been confirmed by morphological evidence. GABAergic terminals have been found in the median eminence near the fenestrated capillaries, suggesting that GABA might be released into the portal blood (96). GABAergic terminals in the median eminence reflect the presence of a tubero-infundibular GABAergic (TI-GABA) system intrinsic to the mediobasal hypothalamus (96). GABAergic inputs to hypothalamic nuclei containing neurosecretory cells have been also demonstrated (96). Thus, GABA can virtually affect hypothalamic-pituitary function either by directly acting on anterior pituitary cells reached through portal

blood flow or by regulating neurosecretory neurons at their nerve endings in the median eminence or at their cell body in hypothalamic nuclei (96). Recent experimental findings support the hypothesis of a direct control exerted by GABA on anterior pituitary cells (86). In fact, GABA of hypothalamic origin has been detected in the hypophyseal portal blood and in the anterior pituitary of rats (86) and GABA binding sites have been described in both rat (40) and human (41) pituitary tissue.

To investigate the involvement of GABAergic system in the regulation of neuroendocrine function, most studies have used GABAergic compounds that act as GABA agonists either directly by activating GABA receptors, or indirectly in several ways (5). A classic direct GABA agonist drug is muscimol (5), but also the GABA derivative, γ -amino- β -hydroxybutyric acid (GABOB), seems to activate GABA receptors (82). As for indirect GABA agonists, baclofen seems to enhance GABA release (5), benzodiazepines seem to displace an endogenous inhibitor of GABA binding (44), while amino oxyacetic acid (AOAA), ethanolamine-O-sulphate (EOS) and sodium valproate (DPA or Na-dipropyl-acetate) act by inhibiting GABA degradation (5,34,37,97).

NEUROENDOCRINE EFFECTS OF GABA AND GABAERGIC COMPOUNDS

Thyrotropin (TSH) and Thyrotropin-Releasing Hormone (TRH)

In rats, GABA (49,99) and GABA agonist drugs (49,67) have been reported to inhibit basal TSH secretion and cold-induced TSH release (66,67). Since GABA is unable to affect TSH release from rat hemipituitaries *in vitro* (49,99), it has been hypothesized that the neurotransmitter inhibits TSH secretion by reducing TRH release at hypothalamic level. The finding that neither GABA nor GABA agonist drugs modify TSH response to exogenous TRH further supports this hypothesis (49,67). Experimental evidence has been also provided for a physiological role of GABA in the control of TSH circadian rhythm in rats (49).

At variance with data in animals, Tamminga et al. (95) showed that oral administration of the GABA agonist, muscimol, did not modify plasma TSH levels in human subjects with Huntington's disease or chronic schizophrenia. Moreover, Melis et al. (70) reported no significant variation of basal serum TSH concentrations after iv injection of the GABA agonist drug, GABOB, in both normal subjects and hypothyroid patients. However, Elias et al. (23) showed that oral treatment with an inhibitor of GABA degradation,

DPA, reduces TSH response to exogenous TRH in both normal subjects and hypothyroid patients. The same authors recently confirmed these findings by using a different GABA agonist compound, baclofen (28), suggesting that in humans GABA exerts an inhibitory effect on TSH secretion by presumably acting at pituitary level (23,28). Thus, the role of GABA in the control of TSH secretion in humans needs further investigation.

Adrenocorticotropin (ACTH) and Corticotropin-Releasing Factor (CRF)

In rats, GABA infused into the third cerebral ventricle, inhibits corticosterone rise induced by surgical stress (64). The administration of the GABA antagonist drugs, picrotoxin and bicuculline, is followed by a significant increase of plasma corticosterone in unstressed animals (64). The inhibition of GABA synthesis reduces the feedback effect of glucocorticoids (2). Single administration of various benzodiazepines induces a clear-cut decrease of ACTH plasma levels without changes in plasma cortisol (12), while chronic treatment with diazepam lowers both plasma ACTH and plasma cortisol (12). These findings strongly suggest an inhibitory role of GABA on ACTH secretion *in vivo*. *In vitro* studies have confirmed this hypothesis showing that GABA blocks CRF release from incubated hypothalamus (47). Moreover, evidence that benzodiazepines inhibit hypothalamic CRF release *in vivo* has been recently provided in rats (63). It seems then possible to assume that in experimental animals GABA exerts an inhibitory control on ACTH secretion by reducing hypothalamic CRF release.

The first data about the effects of GABA on hypothalamic-pituitary-adrenocortical axis in humans were published in 1977 by Melis et al. (68). The authors noted a progressive decrease in plasma cortisol levels after acute iv injection of 50 mg of GABA in normal cycling women during the early follicular phase of the menstrual cycle (Fig. 1). However, Tamminga et al. (95) showed that acute oral administration of the direct GABA agonist drug, muscimol, does not affect cortisol secretion in patients with Huntington's disease or chronic schizophrenia. Takahara et al. (92) reported no significant changes in plasma cortisol after acute subcutaneous (sc) injection of the direct GABA agonist drug, GABOB, in normal men. The same authors (92) also showed that intrathecal injection of GABOB causes an increase in plasma cortisol in cerebrovascular patients. Only recently the findings of Melis et al. (68) were confirmed by Kritzler et al. (57), who observed that chronic treat-

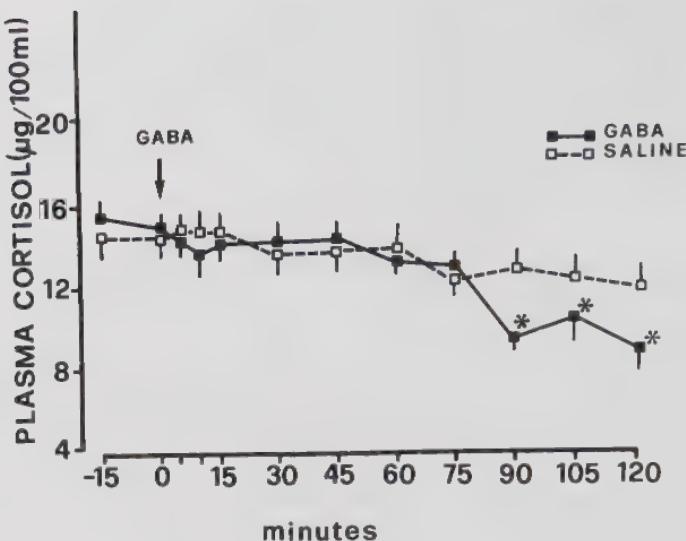


FIG. 1.

The effect of GABA (50 mg, iv bolus) on plasma cortisol concentrations ($M \pm SE$) in five normal women during the early follicular phase of the menstrual cycle. Plasma cortisol shows a significant decrease (* $=p<0.05$) after GABA injection. (Modified from Melis et al., 68)

ment with DPA in children with seizures induced a decrease in plasma ACTH and urinary free cortisol (57). Moreover, acute administration of diazepam significantly lowered plasma ACTH levels in healthy subjects (78; Fig. 2). These data suggest that the activation of endogenous GABAergic system may suppress ACTH secretion in subjects with normal ACTH levels.

An inhibitory effect of chronic DPA treatment on ACTH release has been also demonstrated by several authors in patients with ACTH hypersecretion due to pituitary tumor (17,21,38,45,48,51,52). DPA has then been proposed as a new therapeutic tool for Nelson's syndrome (21,48) and Cushing's disease (51,52). In one patient, a reduction in size of the pituitary adenoma has been also demonstrated after chronic DPA treatment (21), but this finding has not been confirmed by other authors (45,52). As for the site of action of DPA in inhibiting tumoral ACTH hypersecretion, it has been shown that neither DPA nor GABA exert a direct effect on ACTH release from pituitary tumor cells *in vitro* (21,59). Moreover, Gomi et al. (38) reported that in a patient with Nelson's syndrome DPA treatment lowered plasma ACTH levels, but did not alter ACTH

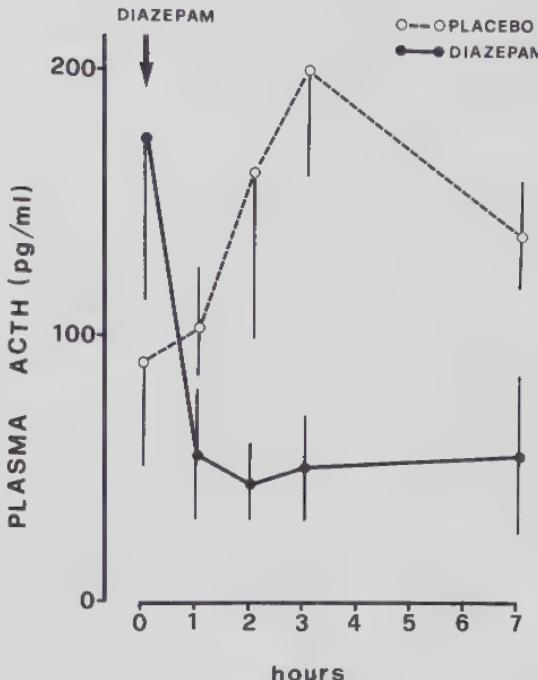


FIG. 2.

The effect of diazepam (7.5 mg, orally) on plasma ACTH concentrations ($M \pm SD$) in five normal subjects. Plasma ACTH shows a significant decrease after diazepam administration.

(Courtesy of Montefrancesco et al., unpublished observations)

response to exogenous CRF. Thus, although a few contrasting data have been published (1,4,24), it seems likely that in humans GABA exerts an inhibitory control over pituitary ACTH secretion by reducing CRF release at hypothalamic level.

Growth Hormone (GH), Somatostatin (SRIF)
and Growth Hormone-Releasing Factor (GRF)

It has been demonstrated that intracerebroventricular (IVT) injection of GABA in conscious ovariectomized (OVX) rats results in a dose-related increase in serum GH (99). An increase in serum GH has been also observed in anesthetized male rats after systemic administration of either the inhibitor of GABA degradation, AOAA, or the GABA metabolite, γ -hydroxybutyrate (GHB) (93,94). Since GABA does not modify GH secretion *in vitro* (99), it has been as-

sumed that the stimulatory effect observed *in vivo* is mediated at hypothalamic level. This hypothesis is supported by the observation that IVT injection of GABA produces a significant increase of hypothalamic SRIF concentrations concomitant to the increase of serum GH levels (93) and that pretreatment with a specific antiserum for rat GRF abolishes GH release induced by GABA (80). Thus, GABA might stimulate GH secretion by reducing hypothalamic SRIF and/or by increasing GRF release (80,93). GABAergic inhibition of SRIF release seems to be mediated through an interaction with dopaminergic system (93), but blockade of DA receptors does not modify GABA-induced GH release (100). A functional interaction of GABA with substance P (94) and an involvement of GABA in the GH-releasing action of opioid peptides (50,80) have been also proposed. A few data suggest that GABA may also inhibit GH release in rats. Fiok et al. (31) showed that in both conscious and anesthetized male rats, the increase of endogenous GABA levels induced by EOS was followed by a decrease of plasma GH. Moreover, systemic administration of muscimol lowered GH levels (86). Thus, the existence of a dual GABAergic control of GH secretion in rats has been hypothesized (86).

In 1977 Melis et al. (68) showed that acute iv injection of GABA enhances plasma GH levels in regularly cycling women during the early follicular phase of their menstrual cycle (Fig.3). Thereafter the GH-releasing effect of acutely administered GABA or GABAergic drugs has been confirmed by several authors. Cavagnini et al. (16) demonstrated that a single oral dose of GABA stimulates GH secretion in humans. Takahara et al. (91,92) observed an increase in plasma GH after iv injection of the GABA metabolite, GHB, in healthy men (91) and after intrathecal injection of the GABA derivative, GABOB, in cerebrovascular patients (92). Fioretti et al. (32) obtained the same stimulatory effect by iv injecting GABOB to healthy women. Tamminga et al. (95) and Koulu et al. (53) demonstrated the GH-releasing effect of the GABA agonist drugs, muscimol (95) and baclofen (53). Finally, acute administration of diazepam was reported to stimulate GH secretion in both healthy subjects (54) and diabetic patients (3). Since the most evident stimulatory effects are exerted by GABAergic compounds that easily cross the blood brain barrier (BBB), such as GHB (91) and baclofen (53), GH-releasing action of GABA agonist drugs in humans seems to be mediated at a central level. Melis et al. (72) supported this hypothesis by showing that GABOB stimulates GH secretion in a dose-dependent manner. In fact, GABOB, which crosses the BBB less easily

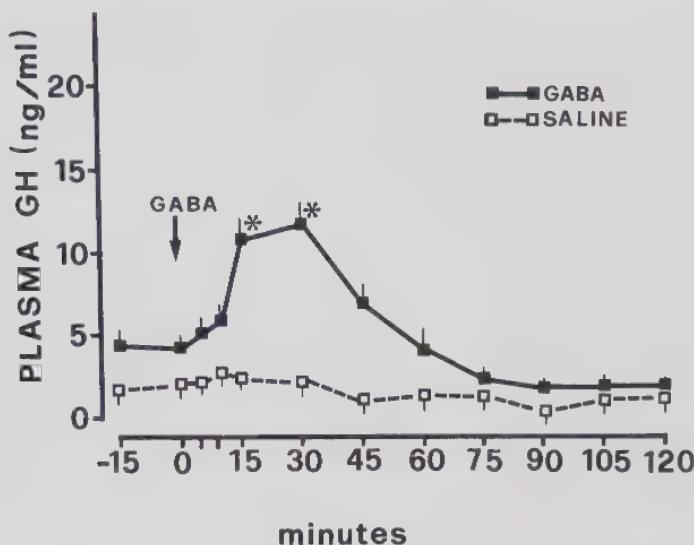


FIG. 3.

The effect of GABA (50 mg, iv bolus) on plasma GH concentrations ($M \pm SE$) in five normal women during the early follicular phase of the menstrual cycle. Plasma GH shows a significant increase (*= $p < 0.05$) after GABA injection. (Modified from Melis et al., 68)

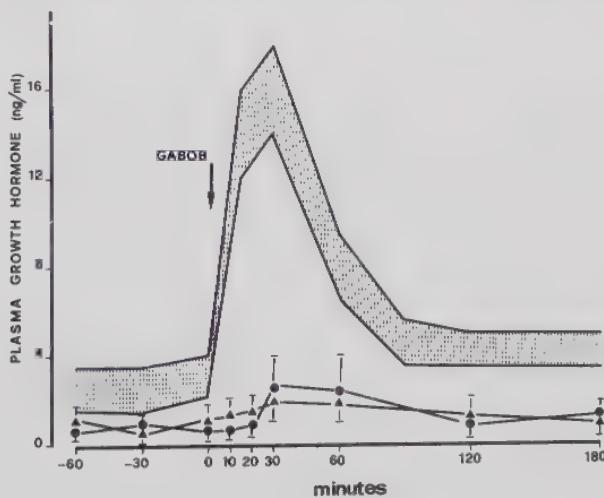


FIG. 4.

The effect of GABOB (100 mg, iv bolus ▲—▲; and 200 mg, iv bolus ●—●) on plasma GH concentrations ($M \pm SE$) in ten hypothyroid patients. Shaded area depicts GH response to 100 mg of GABOB observed in five healthy subjects. GABOB does not modify GH secretion in hypothyroid patients.

than GHB and baclofen, enhanced plasma GH levels in normal women only when it was infused at high doses (100 mg/min and 20 mg/min), while low doses (3.5 mg/min) were unable to affect GH secretion (72). Moreover, high doses of GABOB (100 mg or 200 mg, iv bolus) failed to alter plasma GH levels in hypothyroid patients (Fig.4) who seem to have a dysfunction of hypothalamic centers responsible for the control of GH secretion (11). Finally, pretreatment with the central DA antagonist, pimozide, but not with extracerebral DA inhibitors, such as domperidone and sulpiride, blunted GH release induced by GABA, GABOB or diazepam, suggesting that the GH-releasing activity of GABA is probably due to interactions with dopaminergic system at a site located inside the BBB (15,54,72).

At variance with these findings, an inhibition of stimulated GH release has been also observed after protracted administration of GABAergic drugs; a 3- or 4-day treatment with GABA or baclofen reduced GH response to hypoglycemia, arginine infusion or L-dopa administration (14,16,55). However, contrasting results have been obtained regarding the effects of GABAergic drugs on GH release stimulated by hypoglycemia. A 3-week treatment with the inhibitor of endogenous GABA degradation, DPA, has been reported to have no effect on GH response to insulin-induced hypoglycemia (1), while in our hands a 5-day treatment with GABOB significantly increased GH response to the same stimulus (Fig.5). This discrepancy is probably due to the different activity of the GABAergic drugs used in these studies. Nevertheless, DPA has been shown to blunt almost totally GH release induced by acute diazepam administration (54), further supporting the hypothesis that GABA may play an inhibitory role in the control of GH secretion. As suggested above for the releasing effect of acutely administered GABAergic drugs on basal GH secretion, also the inhibitory action of protracted treatment with GABAergic compounds on stimulated GH secretion seems to be mediated by central interactions with dopaminergic system. In fact, a 3-day premedication with diazepam abolished GH release stimulated by DA agonist drugs (55), but not by α -adrenergic agonists (56). The assumption that both GH-releasing and GH-inhibiting effects of GABA could depend on central interactions with dopaminergic system is apparently contradictory, but it should be kept in mind that GABA may either enhance or inhibit dopaminergic function (18,36,101).

Prolactin (PRL)

The existence of a dual GABAergic control of PRL secretion has

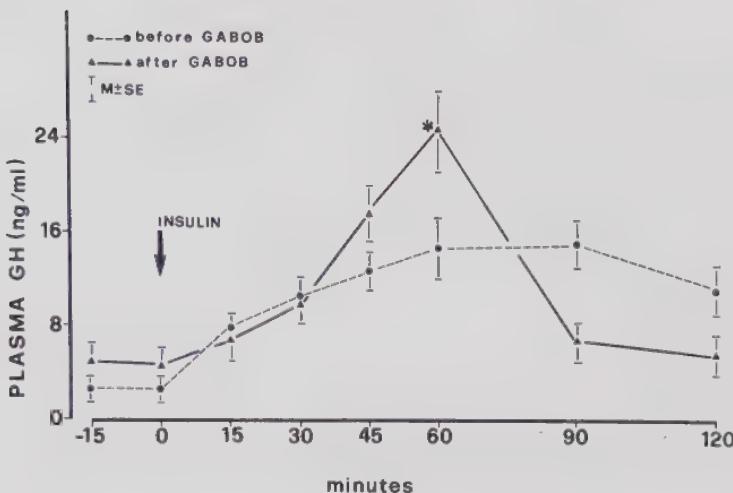


FIG. 5.

The effect of protracted treatment with oral GAEBOB (500 mg/day for 5 days) on GH response to hypoglycemia induced by iv injection of insulin (0.1 IU/Kg) in five normal women during the early follicular phase of their menstrual cycle. After treatment (▲—▲) GH response is significantly greater (*= $p<0.05$) than before treatment (●---●).

been clearly demonstrated in the rat. In fact, IVT injected GABA has opposite effects, low doses suppressing and high doses enhancing plasma PRL levels (98). Moreover, the GABA agonist, muscimol, has been reported to inhibit PRL release after systemic administration and to stimulate it after IVT injection (62). The stimulatory action of GABA on PRL secretion is probably mediated at hypothalamic level by an inhibition of tubero-infundibular dopaminergic (TIDA) system, because IVT injected muscimol induces a significant decrease of pituitary DA concentrations concurrent to the increase of plasma PRL levels (13). An interaction with dopaminergic system has been also proposed to mediate the inhibitory effect of GABA on PRL secretion, since low doses of GABA concomitantly inhibited PRL release and increased DA concentrations at pituitary level (81). However, substantial evidence suggests that GABA inhibits PRL secretion by directly acting at pituitary level. In fact, the reduction in serum PRL induced by IVT injection of an inhibitor of GABA degradation, EOS, is correlated with an increase of GABA concentrations in the hypophysial portal blood and in the anterior pituitary tissue, without any modification of pituitary DA content (43,85). Moreover, GABA inhibits PRL

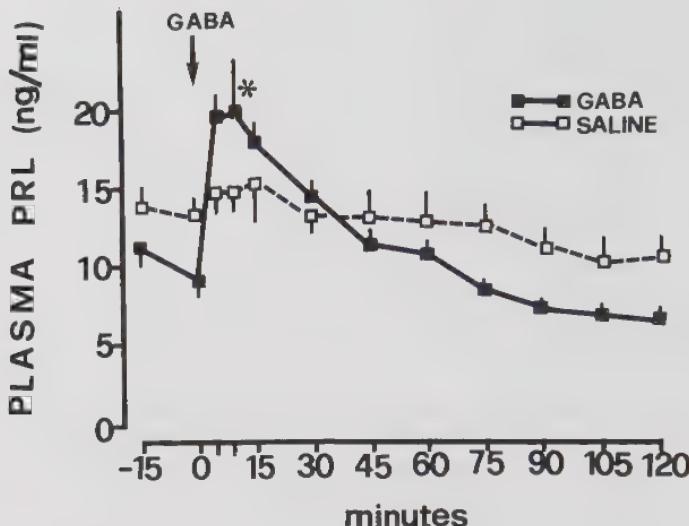


FIG. 6.

The effect of GABA (50 mg, iv bolus) on plasma PRL concentrations ($M \pm SE$) in five normal women during the early follicular phase of their menstrual cycle. Plasma PRL shows a significant increase ($*=p<0.05$) after GABA injection.

(Modified from Melis et al., 68)

release from rat pituitary cells in vitro by acting on specific GABA receptors (29,40,42,58,65,89) and morphological evidence indicates the presence of a TI-GABA system intrinsic to the medio basal hypothalamus (96).

We recently hypothesized the existence of a dual GABAergic control of PRL secretion in humans. The stimulatory component of this dual control was firstly demonstrated by several authors using acute administration of GABA or direct GABA agonist drugs. Takahara et al. (91) showed that iv injection of the GABA metabolite, GHB, stimulates PRL release in healthy male subjects. Tamminga et al. (95) observed a significant increase in mean plasma PRL concentrations after the administration of a single dose of muscimol to patients with Huntington's disease or chronic schizophrenia. Melis et al. (68) and Fioretti et al. (32) respectively described the stimulatory effects of the acute iv injection of pharmacological doses of GABA or GAEBOB to normal women (Fig.6). GABOB was also shown to stimulate PRL secretion after intrathecal injection in cerebrovascular patients, but not after subcutaneous administration in normal men (92). Moreover, the effects of both

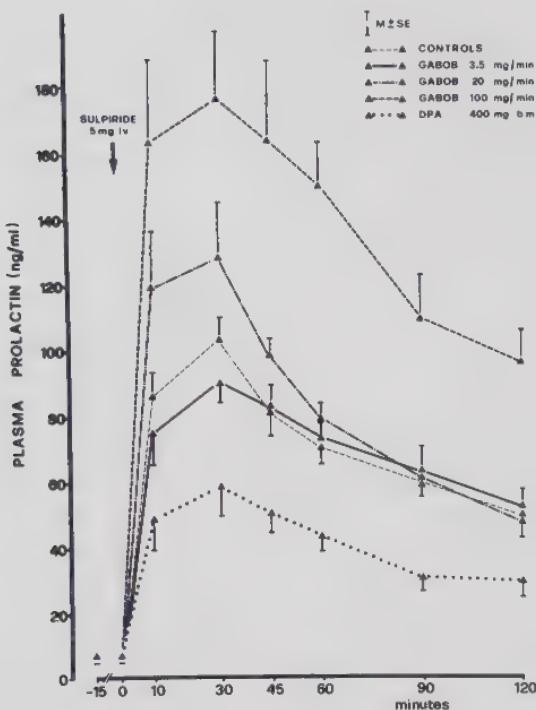


FIG. 7.

The effect of 20 min GABOB infusion at different doses or sodium valproate (DPA) pretreatment on PRL response to sulpiride iv injection. GABOB infusion at the doses of 20 mg/min and 100 mg/min significantly enhances PRL response to sulpiride in a dose-dependent manner. GABOB infusion at the dose of 3.5 mg/min does not modify PRL response. DPA pretreatment significantly reduces PRL response to the same stimulus.

iv GABOB (32) and oral muscimol (95) were dose-dependent. These last findings indicate that in humans PRL response to acute treatment with direct GABA agonist drugs depends both on the dose and on the route of administration of these compounds. The dose-dependence of PRL response to direct GABA agonists was further investigated by Melis et al. (73) who infused different doses of GABOB to normal women over a 20 min period. Only the highest dose of GABOB (100 mg/min) was able to stimulate PRL secretion, while no significant variation in mean plasma PRL levels was observed during the infusion of 20 mg/min and 3.5 mg/min of the GABAergic compound (73). Taken together, the above data strongly suggest that the PRL-releasing effect of GABA agonist drugs is mediated at a central level. In fact, high doses of GABAergic compounds that

do not easily cross the BBB are required to stimulate PRL secretion (32,73,95). As demonstrated in rats, also in humans the stimulatory action of GABA on PRL secretion is probably mediated through dopaminergic system. Melis et al. (69) reported that DA infusion blunts PRL release evoked by iv injection of GABA in normal cycling women. Moreover, Melis et al. (73) showed that iv infusion with high doses of GADOB significantly enhances PRL response to the DA receptor blocking agent, sulpiride (Fig.7). Thus, it seems possible to speculate that both GABA and GADOB might stimulate PRL secretion by affecting endogenous DA release.

The first experimental evidence supporting the existence of an inhibitory action of CAEA on PRL secretion in humans was provided by the observation of Melis et al. (71). Protracted oral administration of GADOB (500 mg/day for 5 days) was shown to blunt PRL response to insulin-induced hypoglycemia. However, PRL response to hypoglycemia has been also reported to be either enhanced or unaffected by protracted administration of different CAAergic drugs (1,14,16). This discrepancy might depend on the interaction of exogenous GABAergic treatment with other neurotransmitter systems that are known to be functionally correlated with the GABAergic one (9,33,36,83,101). To avoid the inconveniences of exogenous GABAergic treatment the effect of the enhancement of endogenous GABA activity on both basal and stimulated PRL secretion was investigated by using the inhibitor of GABA degradation, DPA (74,75,76). A single oral dose of DPA (400 mg) induced a significant decrease of basal PRL levels in normal cycling women during the early follicular phase of menstrual cycle (74, Fig.8). DPA (800 mg, orally) also lowered basal PRL levels in puerperal women (75, Fig.8). As for stimulated PRL secretion, DPA pretreatment (400 mg, orally) blunted PRL response to both central and peripheral DA receptor blockade in normal cycling women (76, Fig.7). Moreover, DPA (800 mg, orally) abolished PRL response to mechanical breast stimulation in puerperal women (75). Since it has been shown that DPA exerts its antiepileptic effects mainly by increasing synaptosomal GABA concentrations (39), the above data indicate that the activation of endogenous CAAergic terminals is followed by an inhibition of both basal and stimulated PRL secretion. Considering that the presence of GABA receptors in human pituitary tissue has been demonstrated by Grandison et al. (41), the analogy between these findings in humans and animal data (see above) strongly suggests that a TI-GABA system may exist also in humans and that endogenous GABA may inhibit PRL release by directly acting at pituitary level.

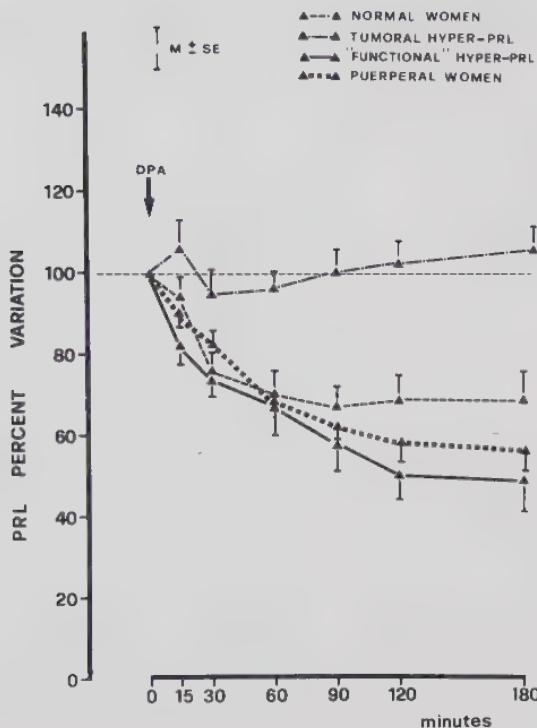


FIG. 8.

The effect of the administration of sodium valproate (DPA) on basal PRL levels in 20 normal women during the early follicular phase of their menstrual cycle, in 8 hyperprolactinemic patients with radiological evidence of pituitary tumor, in 7 hyperprolactinemic patients without evidence of prolactinoma and in 5 puerperal women. The values are expressed as $M \pm SE$ of PRL percent variation over basal concentrations.

We also investigated whether ovarian steroids modulate endogenous GABA activity by administering DPA (400 mg, orally) to regularly cycling women during both early follicular and midluteal phase of the menstrual cycle. DPA-induced PRL decrease resulted to be greater during midluteal than during early follicular phase (Fig. 9), suggesting that GABAergic inhibitory control on PRL secretion is more active when circulating levels of ovarian steroids are higher. Finally, the effects of DPA administration (400 mg, orally) were evaluated in hyperprolactinemic subjects (74). A decrease of plasma PRL levels similar to the one found in normal women was observed in the subjects having no radiological evidence of pituitary tumor (74, Fig. 8). Conversely, no significant

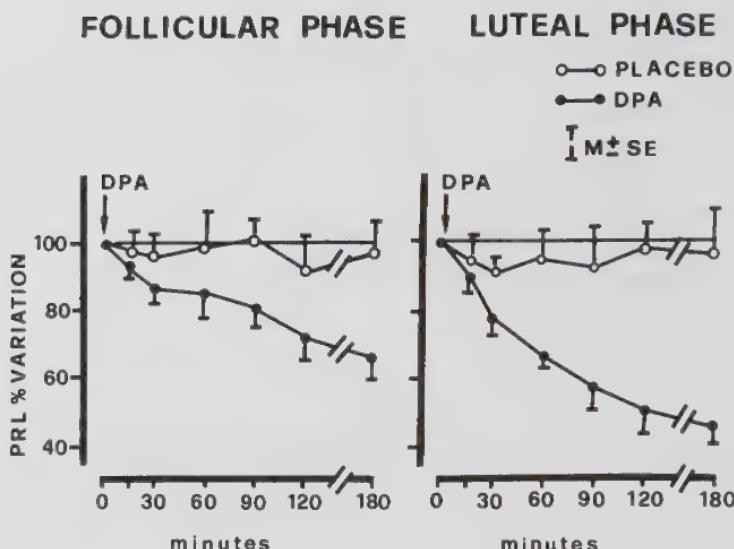


FIG. 9.

Percent variation over basal concentrations ($M \pm SE$) in plasma PRL levels induced by DPA (400 mg, orally) or placebo administration in normal cycling women during early follicular ($n=6$) and mid-luteal ($n=7$) phase. PRL decrease is significantly greater ($p<0.05$) during midluteal than during early follicular phase.

TABLE 1. Plasma PRL levels (ng/ml) observed in 5 women with tumoral hyperprolactinemia before and after iv injection of GABA (50 mg) at 0 min

Subject	time (min)											
	-15	0	5	10	15	30	45	60	75	90	105	120
1	44	41	44	44	48	44	44	44	46	44	40	46
2	31	33	30	28	25	25	28	23	29	28	28	28
3	50	51	48	45	43	46	45	48	39	42	43	46
4	72	70	65	68	74	58	64	60	72	70	65	68
5	48	44	48	48	47	52	44	46	44	48	52	44

modification of PRL secretion was detected in patients with prolactinoma (74, Fig. 8). Thus, tumoral hyperprolactinemia seems to be independent on the inhibitory GABAergic control and it may be hypothesized that a functional defect of endogenous GABAergic system exists in such condition as already demonstrated for other hypothalamic neurotransmitters (79). On the other hand, abnormalities of the GABA-receptors system at pituitary level may also exist. However, the inability of iv injected GABA (50 mg) to stimulate PRL release in patients with prolactinoma (Table 1) favors the hypothesis of a functional defect of hypothalamic neurotransmitter systems in these patients.

The finding that DPA administration was able to lower PRL release only in non-tumoral hyperprolactinemia offered some interesting perspectives for the clinical application of a "DPA test" to differentiate between tumoral and functional hyperprolactinemia. A study was then carried out in 33 hyperprolactinemic women to check whether PRL response to DPA (400 mg, orally) correlated with PRL response to other compounds having well documented effects on PRL secretion in both normal and hyperprolactinemic subjects. Sulpiride (5 mg, iv bolus), TRH (200 µg, iv bolus), nomifensine (200 mg, orally) and DPA were then administered to the same subjects in a randomized order. In subjects with tumoral hyperprolactinemia, no significant modification of plasma PRL levels was observed following the administration of the four drugs (Fig. 10). Conversely, in patients with functional hyperprolactinemia, sulpiride and TRH induced a significant increase in PRL concentrations, while nomifensine and DPA significantly reduced PRL release (Fig. 10). Moreover, plasma PRL decrements following DPA administration were significantly correlated with either PRL decrements following nomifensine or PRL increments following sulpiride or TRH administration. Thus, the ability of DPA test to discriminate between functional and tumoral hyperprolactinemia resulted to be significantly correlated ($p < 0.01$) with the one of nomifensine, sulpiride and TRH.

Gonadotropins and Gonadotropin-Releasing Hormone (GnRH)

A stimulatory effect on LH secretion was firstly observed in rats after IVT injection of high doses of GABA (83, 84, 98, 100). This effect appeared to be mediated at a central level (83), but not through interactions with dopaminergic system (100). However, in male rats, GABAergic stimulation of LH secretion was only observed concomitantly to pentobarbital anesthesia (84).

Recent data have demonstrated that GABA may also have an inhib-

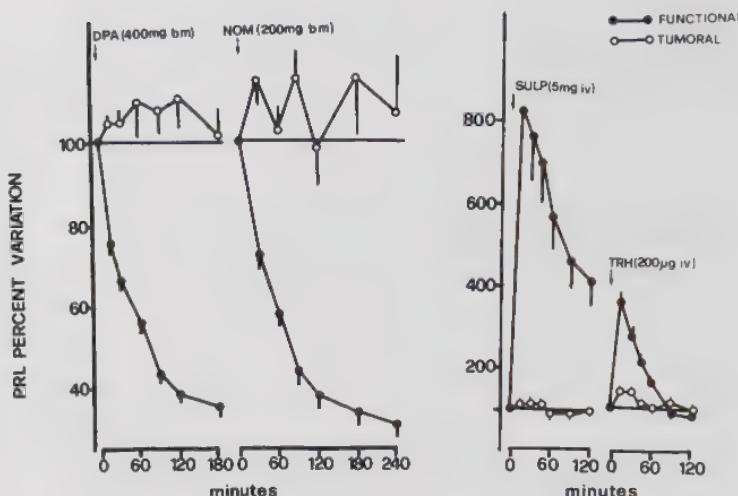


FIG. 10.

The effect of the administration of sodium valproate (DPA), nomifensine (NOM), sulpiride (SULP) and TRH on plasma PRL levels in patients with tumoral ($n=8$; ○—○) or functional ($n=25$; ●—●) hyperprolactinemia. The values are expressed as $M \pm SE$ of PRL percent variation over basal concentrations.

itory action on gonadotropin release in rats. In fact, GABAergic drugs have been reported to block ovulation in female (7,8), to decrease testicular weight in male (19) and to inhibit LH secretion in OVX rats (20,35,60). This inhibitory action of GABA is exerted at a central level, since GnRH administration counteracts the ovulatory blockade induced by GABAergic treatment (7) and GABAergic compounds do not affect LH response to exogenous GnRH (20). It was firstly proposed that GABA could indirectly reduce endogenous GnRH release by inhibiting noradrenergic transmission (35,60), but morphological evidence has been recently provided suggesting that GABAergic neurons may directly modulate the activity of GnRH-secreting cells (46,61). An involvement of GABA in the negative feedback action of estradiol has been then postulated. This hypothesis has been further supported by the finding that castration causes a decrease in GABA synthesis in several brain regions and that estradiol substitution reverses castration effects (22). Moreover, labelled estradiol has been located in GABAergic neurons after its injection to rats (87).

In humans, endogenous GABA activity is also modulated by ovarian steroids (Fig.9) and this could account for the inability of

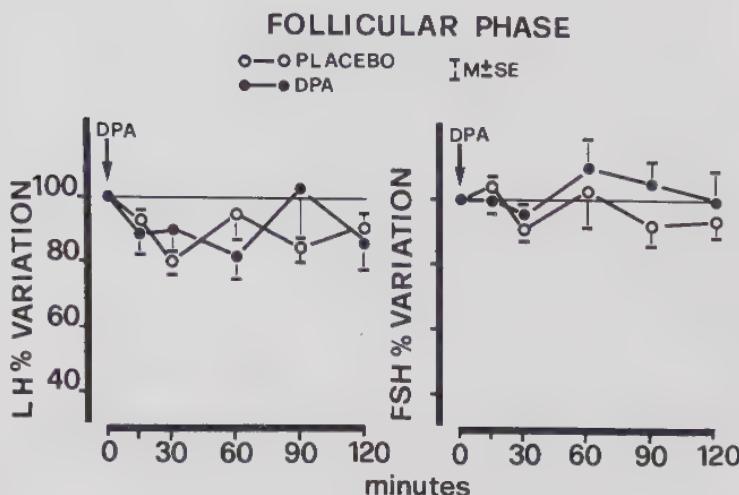


FIG. 11.

The effect of the oral administration of 400 mg of sodium valproate (DPA) on LH and FSH secretion in 6 normal women during the early follicular phase of their menstrual cycle. No significant changes in both LH and FSH secretion are induced by DPA or placebo administration. The values are expressed as $M \pm SE$ of gonadotropin percent variation over basal concentrations.

(Modified from Melis et al., 77)

exogenous GABA (50 mg, iv bolus) to alter gonadotropin secretion during the early follicular phase of the menstrual cycle (68).

To investigate whether endogenous GABAergic system participates in the control of gonadotropin secretion throughout the menstrual cycle, DPA (400 mg, orally) was administered to regularly cycling women during both early follicular and midluteal phases (77). During early follicular phase, no significant changes in basal gonadotropin levels were observed after DPA or placebo administration (Fig. 11). Conversely, during midluteal phase DPA administration induced a significant fall in plasma LH concentrations that were reduced by 40% after 120 min (Fig. 12). Basal plasma FSH levels were unaffected by DPA treatment in both early follicular and midluteal phase (Figs. 11 and 12). The effect of DPA pretreatment (400 mg, orally) on gonadotropin release stimulated by exogenous GnRH (10 µg, iv bolus) was also studied (77). During both early follicular and midluteal phase, DPA did not modify gonadotropin response to exogenous GnRH (Fig. 13). These findings strongly suggest that during the estrogen-progesterone (midluteal) phase of the menstrual cycle, endogenous GABA is involved in the inhibi-

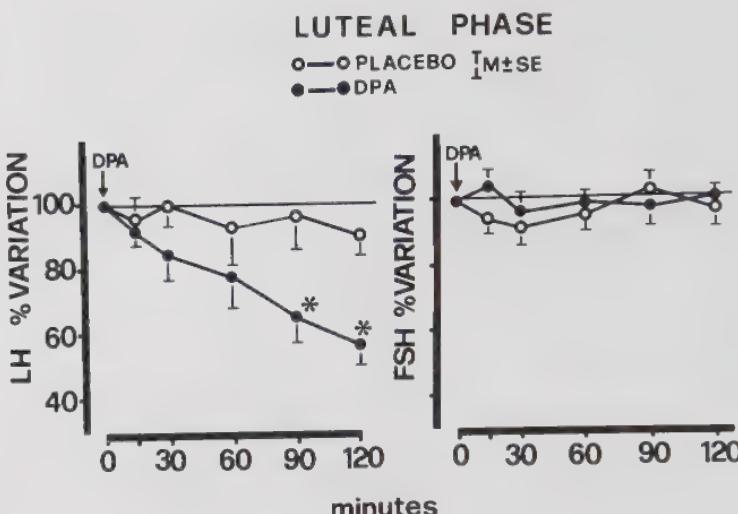


FIG. 12.

The effect of the oral administration of 400 mg of sodium valproate (DPA) on LH and FSH secretion in 7 normal women during the midluteal phase of their menstrual cycle. DPA administration induces a progressive decrease of plasma LH levels that become significant at 90 min ($*=p<0.05$), but does not modify FSH secretion. The values are expressed as $M \pm SE$ of gonadotropin percent variation over basal concentrations. (Modified from Melis et al., 77)

tory control of LH secretion at a central level. In agreement with animal data (see above) it could then be hypothesized that also in humans a GABAergic mechanism participates in the hypothalamic component of the negative feedback action exerted by ovarian steroids on LH secretion.

Contrasting results have been reported by Elias et al. (26) who showed that protracted treatment with DPA did not affect basal gonadotropin secretion, but reduced LH response to exogenous GnRH (100 μ g). However, the same authors (27) also reported that protracted treatment with a different GABAergic drug, baclofen, did not modify LH response to 100 μ g of GnRH. Moreover, they also observed an enhancement of LH response to the same dose of GnRH after a 3-day treatment with DPA in patients with chronic renal failure (25). Thus, data obtained by using maximal doses of GnRH (100 μ g) do not seem to be reproducible. However, the different preexistent endocrine conditions may influence LH response to GnRH after DPA treatment.

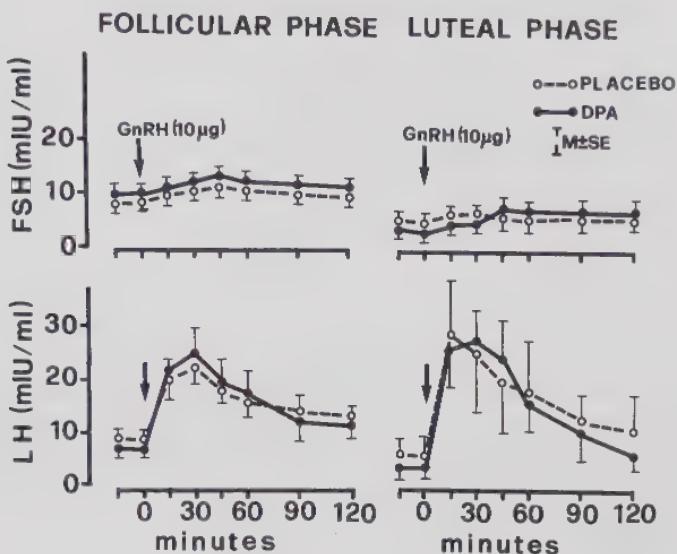


FIG. 13.

The effect of pretreatment with sodium valproate (DPA; 400 mg, orally) on LH and FSH response to exogenous GnRH (10 µg, iv bolus) in 5 normal women during the early follicular phase and in 5 normal women during the midluteal phase of their menstrual cycle. DPA administration does not modify gonadotropin response to exogenous GnRH. (Modified from Melis et al., 77)

CONCLUSION

Experimental evidences suggest that endogenous GABA is involved in the regulation of hypothalamic-pituitary function not only in rats, but also in humans. The participation of GABAergic system in the control of both ACTH and PRL secretion has been clearly demonstrated, while the elucidation of neuroendocrine mechanisms mediating GABA action on TSH, GH and gonadotropin secretion needs further investigation. The interpretation of the results obtained so far is difficult because of the variety of GABAergic drugs and experimental approaches used by different authors. Moreover, the administration of direct GABA agonist drugs leads to interactions with other neurotransmitter systems that are functionally linked to the GABAergic one. Since GABA antagonists are not suitable for human studies because of their convulsant effect, future researches aiming at clarifying the physiological neuroendocrine role of GABA will depend on the availability of indirect GABA agonist drugs activating endogenous GABAergic synapses.

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