

REVIEW

Chaste tree (*Vitex agnus-castus*) – Pharmacology and clinical indications

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Summary

Extracts of the fruits of chaste tree (*Vitex agnus castus* = AC) are widely used to treat premenstrual symptoms. Double-blind placebo-controlled studies indicate that one of the most common premenstrual symptoms, i.e. premenstrual mastodynia (mastalgia) is beneficially influenced by an AC extract. In addition, numerous less rigidly controlled studies indicate that AC extracts have also beneficial effects on other psychic and somatic symptoms of the PMS. Premenstrual mastodynia is most likely due to a latent hyperprolactinemia, i.e. patients release more than physiologic amounts of prolactin in response to stressful situations and during deep sleep phases which appear to stimulate the mammary gland. Premenstrually this unphysiological prolactin release is so high that the serum prolactin levels often approach heights which are misinterpreted as prolactinomas. Since AC extracts were shown to have beneficial effects on premenstrual mastodynia serum prolactin levels in such patients were also studied in one double-blind, placebo-controlled clinical study. Serum prolactin levels were indeed reduced in the patients treated with the extract. The search for the prolactin-suppressive principle(s) yielded a number of compounds with dopaminergic properties: they bound to recombinant DA₂-receptor protein and suppressed prolactin release from cultivated lactotrophs as well as in animal experiments. The search for the chemical identity of the dopaminergic compounds resulted in isolation of a number of diterpenes of which some clerodadienols were most important for the prolactin-suppressive effects. They were almost identical in their prolactin-suppressive properties than dopamine itself. Hence, it is concluded that dopaminergic compounds present in *Vitex agnus castus* are clinically the important compounds which improve premenstrual mastodynia and possibly also other symptoms of the premenstrual syndrome.

Key words: Chaste tree, prolactin, dopamine, premenstrual symptoms, mastodynia

■ Introduction

Many premenstrual symptoms, particularly premenstrual mastalgia (mastodynia) are associated with latent hyperprolactinemia (Jarry et al. 1994; Wuttke et al. 1997; Jarry et al. 1999). These patients do not suffer from prolactinomas but in response to daily stressful events they hypersecrete prolactin which appears to stimulate the mammary gland thereby causing masto-

dymia. During the premenstrual time these patients have often chronically elevated serum prolactin levels (Jarry et al. 1999). Pituitary prolactin release is under tonic hypothalamic inhibition by dopamine (DA) which is secreted by the tuberoinfundibular DA neurons into the portal vessels which connect the hypothalamus with the pituitary. Hence, it was concluded that particularly dur-

ing the premenstrual period this dopaminergic inhibition is insufficient such that under stressful daily stimuli hyperprolactinemia occurs. Consequently, mild inhibition by dopaminergic agents was proposed to be efficient in the treatment of premenstrual mastalgia. Indeed, a synthetic dopamine agonist (bromocriptin) had also beneficial effects on breast pain, tenderness and heaviness and this improvement was associated with reduced serum prolactin levels (Mansel and Dogliotti, 1990). Not only premenstrual mastalgia but also other somatic and psychic premenstrual symptoms such as premenstrual depression, sadness, irritability, emotional reactivity, and sensoric sensitivity were improved by another synthetic dopamine agonist lisuride (Schwibbe et al. 1983). Hence, it appears that also a slight underfunction of other dopaminergic brain structures such as the nigrostriatal and the mesolimbic systems, may be causally linked to premenstrual symptoms. Clinical experience indicated that not only premenstrual mastalgia but also cycle irregularities can be effectively treated with extracts of *Vitex agnus castus* (AC) (Milewicz et al. 1993; Roeder, 1994; Lauritzen et al. 1997; Gerhard et al. 1998; Halaska et al. 1999). We proposed therefore that the AC extracts contain dopaminergic compounds (Jarry et al. 1991; Jarry et al. 1994). In the pharmacological and clinical studies described below the AC extract BNO 1095 (a 70% ethanol, 30% H₂O extract, Bionorica, Neumarkt, Germany) was routinely used; this is also the preparation for the production of the commercially available tablet and liquid preparation of Agnucaston®.

Material and Methods, Results and Discussion

In the past we looked for dopaminergic compounds in this extract and were indeed able to identify several fractions which bound to recombinant DA receptors and which were inhibitory to pituitary prolactin release. Dopaminergic activities were present in polar and unpolar fractions. Ethanol/water (50:50) extractable dopaminergic compounds could be separated by molecular weights and yielded 3 fractions (P1, P2 and P3). When in vitro dopamine receptors are incubated with radioactively labelled ligands binding to these receptors, such as sulpiride, the compounds in all 3 fractions displaced the radioactive receptor ligand dose-dependently and this yielded 3 peaks with dopamine receptor binding activity of which P3 constituted the majority of substances (Fig. 1). In the in vitro experiments dispersed pituitary cells were cultivated and they secreted high amounts of prolactin since the culture medium did not contain any dopaminergic activity. When dopamine or dopaminergic compounds

were added, prolactin secretion by the lactotrophs was dose-dependently inhibited. As in the radioreceptor assay P3 was the most potent fraction to inhibit prolactin secretion (Fig. 2). An attempt to purify the(se)

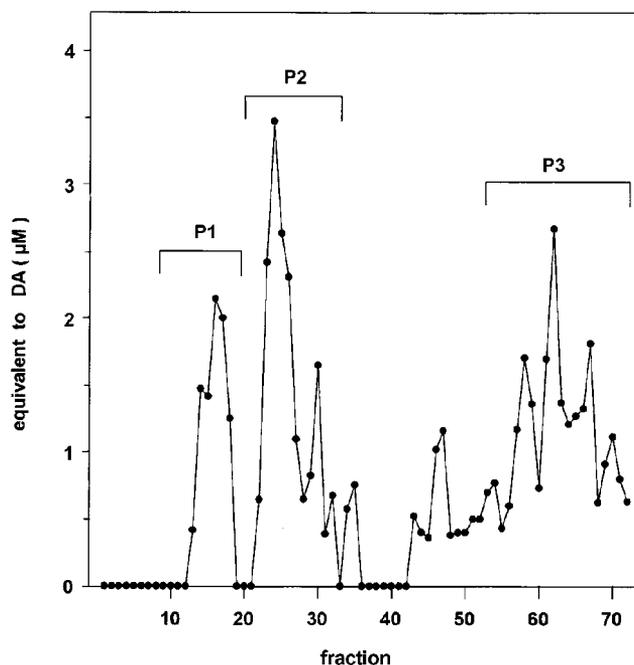


Fig. 1. FPLC-chromatography on a superose-12-column of an aqueous/ethanolic extract (50/50 VOL) yielded 3 peaks which bound to the dopamine receptor-2-type. The fractions under the horizontal brackets were combined and constituted peak 1, peak 2 and peak 3 (P1, P2 and P3, respectively).

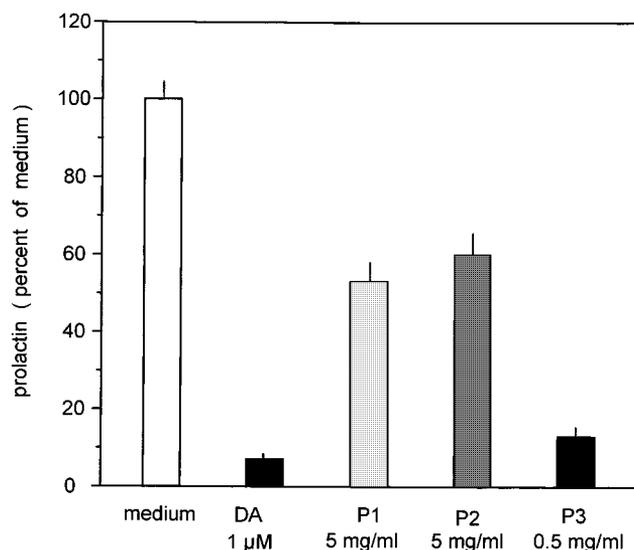


Fig. 2. P1, P2 and P3 (see Fig. 1) were inhibitory to prolactin release from dispersed rat pituitary cells. Dopamine at 10⁻⁶ M was used for comparison. Note that P3 concentrations were 10-fold lower than P1 and P2 concentrations.

substance(s) out of P3 failed since any purification step was counteracted by a high degree of lability of the substance(s); the dopaminergic activity disappeared which may either be due to high degree of thermolability or due to condensation of the molecules (Wuttke et al. 1995). In earlier attempts to purify dopaminergic compounds from *Vitex agnus castus* extracts (BNO1095), we and others were successful to identify a number of diterpenes (Christoffel et al. 1999; Hoberg et al. 1999). Prominent diterpenes found in *Vitex agnus castus* extract are rotundifuran (P-107) and 6 β , 7 β -diacetoxy-13-hydroxy-labda-8,14-diene (=B 110). These two compounds were also described by Hoberg et al. (1999). In addition to these diterpenes we identified 3 more compounds of the labdane type of which the structure and their chemical names are given in Fig. 3. Recently we succeeded to chemically identify the most active substances in the unpolar fractions of BNO1095. The proposed structures of the substances are shown in Fig. 4. Six closely related diterpenes with a clerodane skeleton of which 5 have the structure of a cleroda-x,14-dien-13-ol and one has the structure of a cleroda-x,y-14-trien-13-ol have been identified. The

final structures of these compounds including the absolute stereochemistry await clarification to verify the exact position of the double bonds in ring A or B, respectively.

These substances were tested for their activity in the dopamine receptor assay (Fig. 5). The most potent compound was B115 of which 1 μ M had a binding activity equivalent to 218 nM DA. Hence, dopamine was approximately 4-5-fold more active to displace its radioactive ligand from the D2 receptor preparation than B115. The clerodadienols were slightly less potent than B115. The potency was approx. 1/8 of that of dopamine) but as shown in Fig. 6 their amount in a gram of the dried *Vitex agnus castus* extract was so high that its total dopaminergic activity was approx. 5.7-fold higher than that of B115. In fact, the total dopaminergic activity of the clerodadienols represented more than 50% of all dopaminergic activities of the other compounds. Hence, the major dopaminergic compounds in the BNO1095 *Vitex agnus castus* extract are the clerodadienols.

The clerodadienols are also potent inhibitors of prolactin release. At concentrations of 86-fold higher mo-

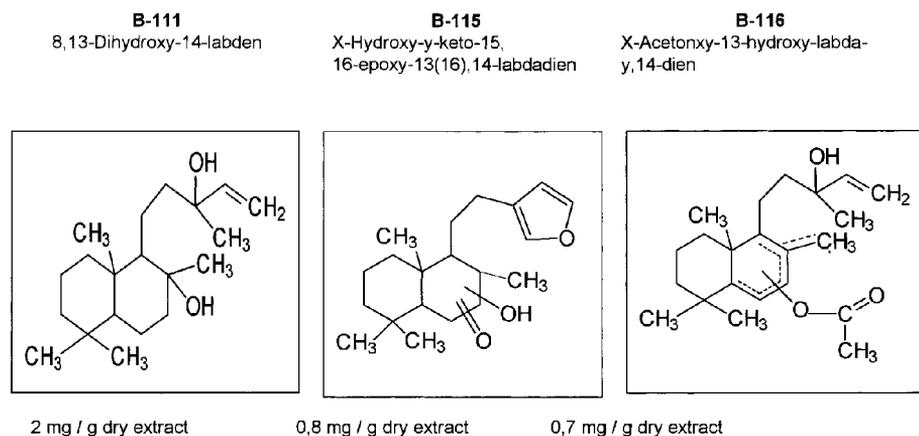


Fig. 3. Diterpenes with biological activity isolated from *Agnus castus*.

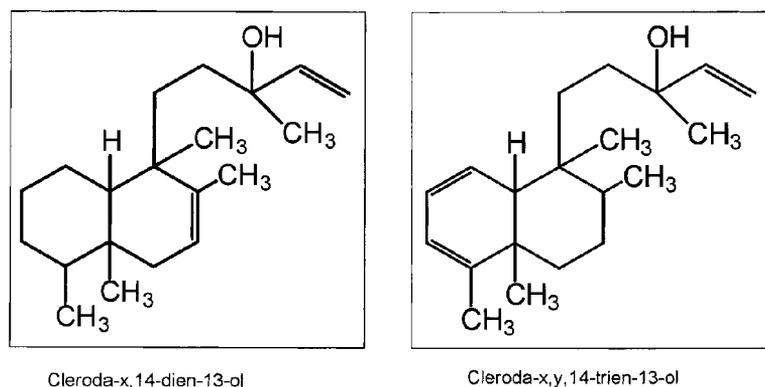


Fig. 4. Composition and structure of the isolated BNO – diterpenes six closely related diterpenes with the clerodane – skeleton were isolated of which – five compounds had the structure of clerodadien-13-ol (MW 290) – one compound had the structure of cleroda-trien-13-ol (MW 288).

larity than dopamine they inhibited prolactin release more profoundly than 10^{-6} M dopamine. Half of the concentration (43-fold more than dopamine on the molar basis) of the clerodadienols were slightly less ef-

fective than 10^{-6} M dopamine (Fig. 7). The release of prolactin by the lactotrophs was stimulated by high intracellular cAMP levels. Dopamine acts via a dopamine-inhibited adenylate cyclase, hence, it in-

Fig. 5. Specific activity of AC-compounds in the D2-receptor assay. Each compound was tested in 1 μ mol concentration. The numbers on top of each bar indicate the displacement properties given in nmol of dopamine and standard errors of the mean (S.E.M.) are given on top of each bar.

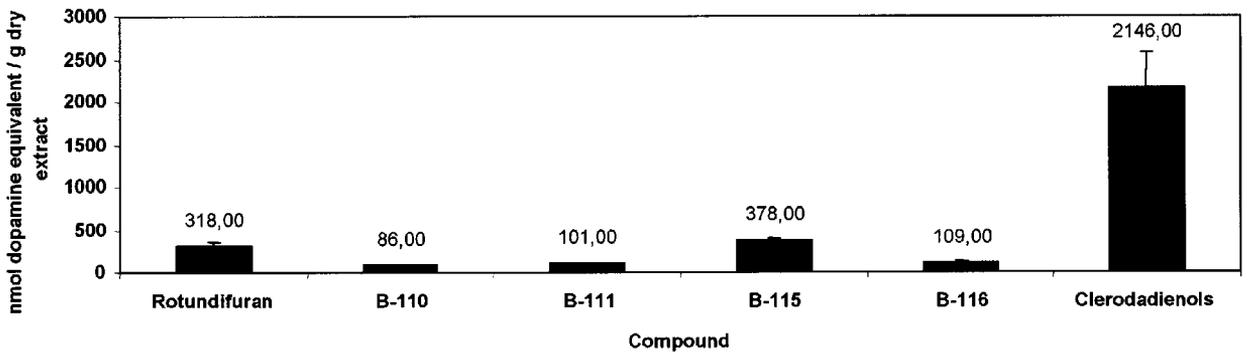
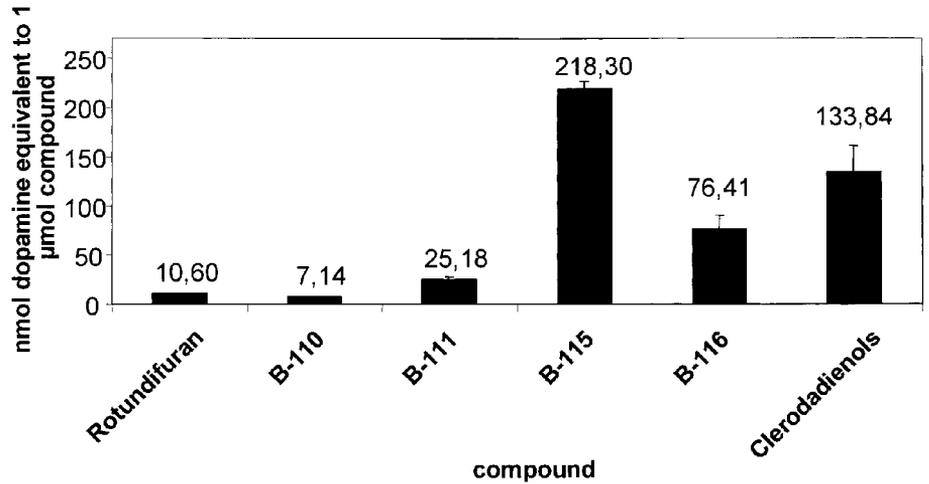


Fig. 6. Total dopaminergic activity of various diterpenes in the D2-receptor assay (nmol dopamine equivalent/g dry extract) and standard errors of the mean (S.E.M.) are given on top of each bar.

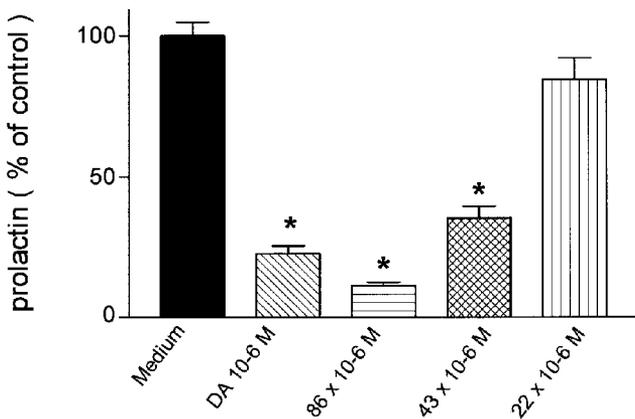


Fig. 7. Effects of clerodadienols on in-vitro prolactin release. Basal prolactin concentrations in the supernatants were set 100%. Standard errors of the mean (S.E.M.) are given on top of each bar. Asterisks indicate $P < 0.05$.

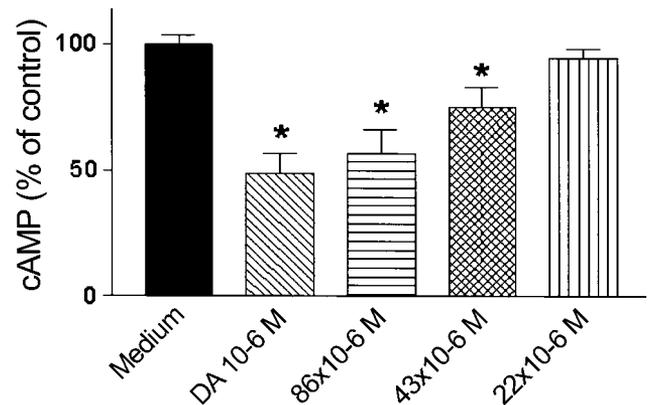


Fig. 8. Effects of clerodadienols on in-vitro cAMP under stimulation with 1 μ M forskolin. Standard errors of the mean (S.E.M.) are given on top of each bar. Asterisks indicate $P < 0.05$.

hibits cAMP production. Forskolin is a stimulator of cAMP production and therefore stimulates pituitary prolactin release. As shown in Fig. 8 this forskolin-stimulated cAMP release could be effectively inhibited by dopamine and by the clerodadienols. Again, the clerodadienols were approx. equipotent to dopamine at an approx. 50-fold higher concentration.

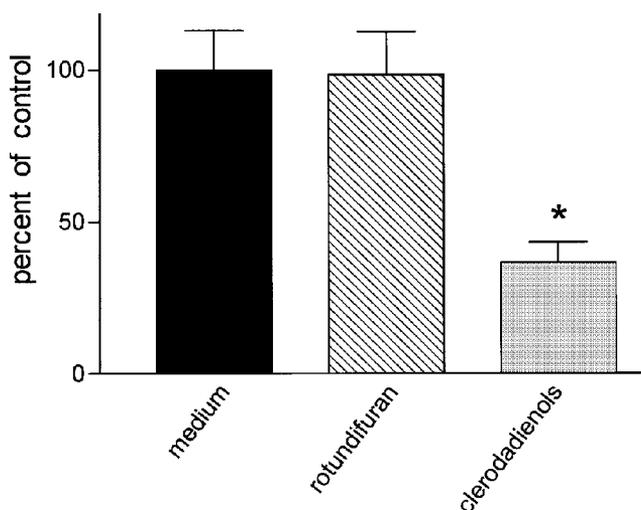


Fig. 9. Inhibition of prolactin release by clerodadienols isolated from *Vitex agnus castus* at concentrations of 20 µg/ml. Note that at this workstation rotundifuran was ineffective while the clerodadienols inhibited prolactin release significantly. Standard errors of the mean (S.E.M.) are given on top of each bar. Asterisks indicate $P < 0.05$.

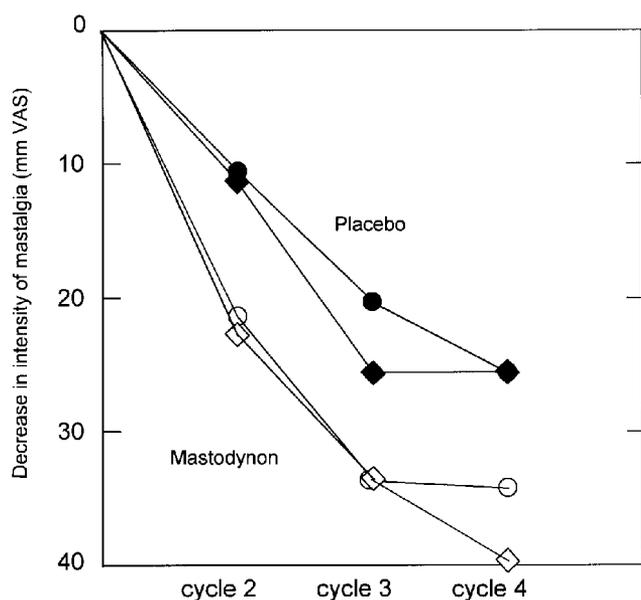


Fig. 10. Decrease in intensity of mastalgia under Mastodynon® – comparison of the results of Wuttke et al. 1997 and Halaska et al. 1999.

Fig. 9 details that rotundifuran, the first of the published diterpenes with dopaminergic activities (Hoberg et al. 1999) at a concentration at which the clerodadienols were highly potent to inhibit prolactin release, was without any effect on the secretion of this hormone by the lactotrophs.

Since the clerodadienols are very stable and resistant to almost any treatment, this contrasts the stability of dopamine and other dopaminergic compounds. Hence, it can be concluded that the major dopaminergic activities in *Vitex agnus castus* preparations are diterpenes of which the clerodadienols exert the most prominent dopaminergic activity.

Solid clinical data concerning the effects of AC preparations on premenstrual symptoms or on pituitary prolactin release are scarce. Most studies published hitherto were either not blinded and/or not placebo-controlled.

In two recent clinical studies the efficacy of the commercially available *Vitex agnus castus* extract to effectively reduce premenstrual mastodynia was established. These patients had to complete a visual analogue scale (VAS) in which their breast pain could be rated from 0 mm (lowest breast pain) to 10 mm (ex-

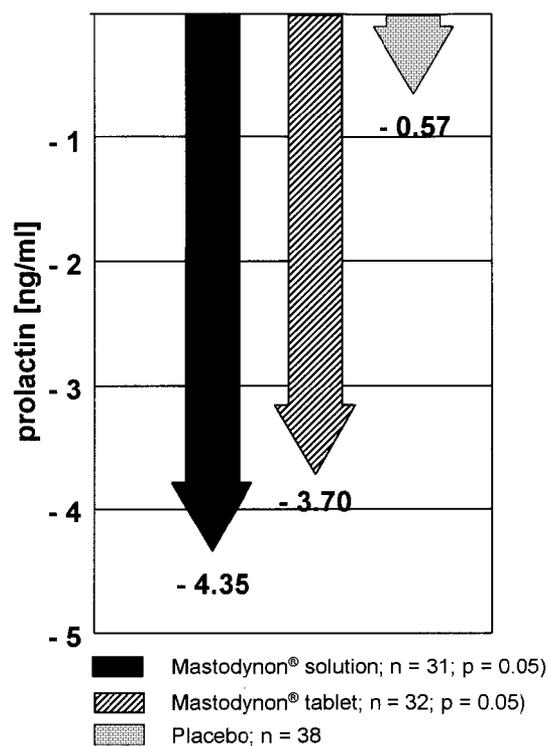


Fig. 11. Treatment of cyclical mastalgia: Change of basal prolactin secretion after three cycles. Compared to placebo, the basal prolactin levels were significantly decreased in the active treatment groups (Wuttke et al. 1997).

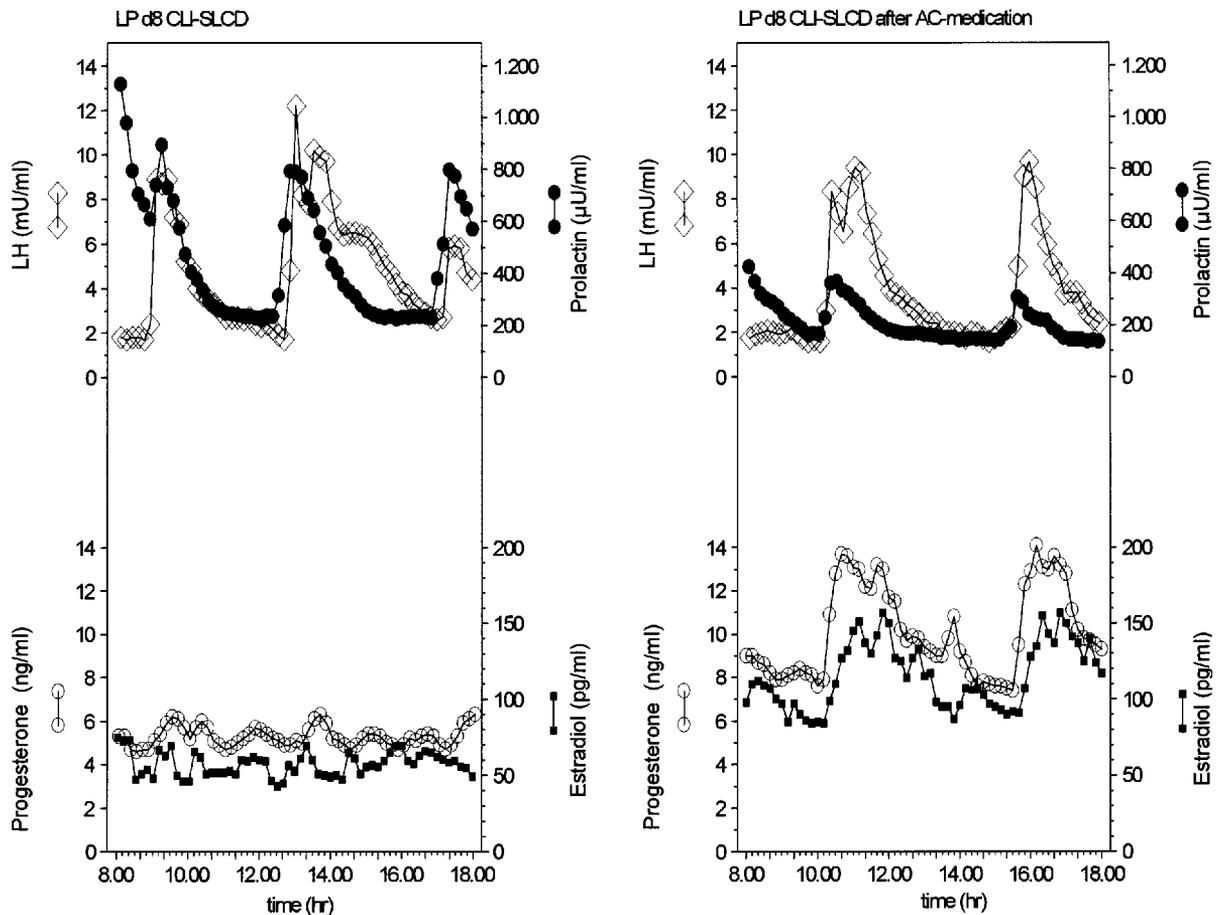


Fig. 12. Example of a woman suffering from latent hyperprolactinemia associated with a corpus luteum deficiency. In the initial 12 h investigation period (no treatment left part) she responded to the stress of veinipuncture with a transient hyperprolactinemia and also the LH pulse associating prolactin pulses are very high. During this cycle progesterone levels were in the corpus luteum deficiency range and the LH pulses did not result in increased progesterone secretion. In contrast, after 3 months treatment with a commercially available AC preparation (Mastodynon®) the stress-induced and LH pulse-associated prolactin pulses were reduced. Mean serum progesterone levels were higher and each LH pulse causes increased luteal progesterone and estradiol secretion.

tremely strong breast pain). Results of this self-scoring are shown in Fig. 10. Both preparations (Mastodynon tablets and solution) reduced the mastalgia score by 35–40%, an effect significantly stronger than that of placebo (25%). (Wuttke et al. 1997; Halaska et al. 1999). In one of these studies (Wuttke et al. 1997) the AC preparation was also shown to reduce serum prolactin levels (Fig. 11). Recently we succeeded to take frequent blood samples from patients suffering from premenstrual mastodynia. These patients received an indwelling antecubital vein catheter and blood samples were withdrawn immediately thereafter at 10 min intervals for a period of 10 h. The data for one of these patients are shown in Fig. 12. As a result of the stress of veinipuncture this patients' pituitary released large

amounts of prolactin resulting in prolactin levels which were clearly in the pathological range. During the luteal phase LH pulses occur at relatively regular 3 to 4 h intervals which were also seen in this patient. These LH pulses were associated by prolactin pulses of which the peak values were also clearly in the pathological range. In this patient serum progesterone and estradiol levels were in a range which indicated a corpus luteum deficiency. After a 3-months-treatment with the commercially available *Vitex agnus castus* preparation Mastodynon the supraphysiological release of prolactin due to stress and the prolactin pulses associated with LH pulses had normalized and as a result the LH pulses did now induce increased progesterone and estradiol levels and also basal progesterone and estra-

Dopaminergic Systems

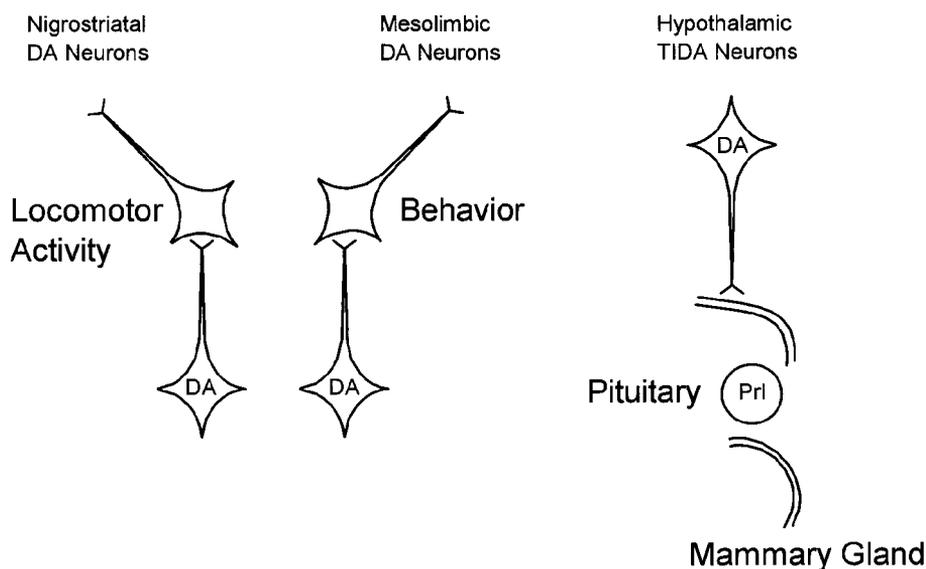


Fig. 13. The 3 important brain dopaminergic systems are depicted. The nigrostriatal system is involved in the regulation of locomotor activity. The mesolimbic dopaminergic system regulates behaviour. The tuberoinfundibular dopaminergic system of the hypothalamus releases dopamine into the portal vessels and thereby inhibit pituitary prolactin release.

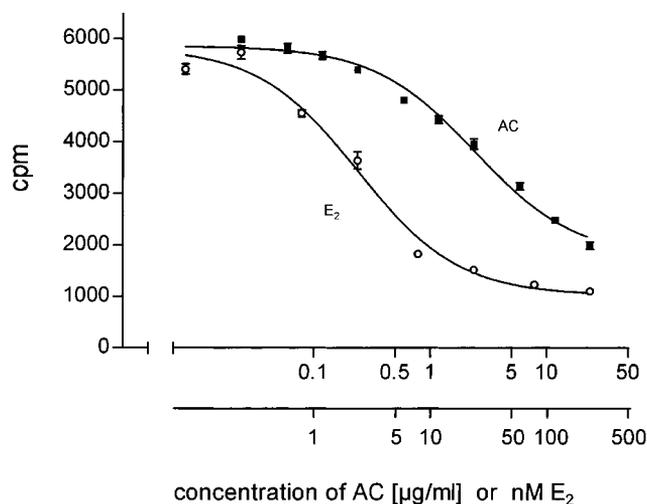


Fig. 14. The *Vitex agnus castus* extract displaces radioactively labelled estradiol from cytosolic estrogen receptors prepared from human endometrium. Hence, substances present in this preparation compete with the estradiol for estrogen binding sites (receptors).

diol levels were in the normal range. Details about copulsatility of LH and prolactin and the importance of LH and prolactin pulses were recently reviewed by Wuttke et al. (2001).

The fact that these diterpenes address the dopamine-2-receptor types and thereby inhibit pituitary prolactin release and that they are highly lipophilic suggests that they may easily pass the blood/brain barrier. Hence, they will have access to other brain dopaminergic sys-

tems and their postsynaptic receptors which form the nigrostriatal and mesolimbic dopaminergic systems (Fig. 13). These systems are involved in the regulation of locomotor activity and behaviour. Hence, the beneficial effects of *Vitex agnus castus* extracts, particularly of therein found diterpenes may stimulate these postsynaptic receptors and thereby modulate the often observed locomotor unrest and behavioural instability.

It is a clinical observation that *Vitex agnus castus* extracts may also be beneficial in the treatment of climacteric complaints. Therefore, we studied the extract BNO1095 for putative estrogenic activities. Indeed, *Vitex agnus castus* extracts contained substances which displaced radioactively labelled estradiol from a cytosolic estrogen receptor preparation (Fig. 14). The message "estrogen" is received by intracellular receptors of which two have been cloned. The old, well-characterized estrogen receptor is now called the estrogen receptor α (ER α). The new estrogen receptor is the ER β (Kuiper et al. 1996). The functions of the ER α are relatively well-defined: In the uterus, myo- and endometrial proliferation are stimulated; in the bone, the osteoporosis-preventing effects of estradiol are mediated via the ER α and putatively protective effects in the cardiovascular system appear also to be mediated via the ER α (for review see Couse and Korach, 1999). Much less is known about the physiological significance of the ER β . According to Gustafsson and his coworkers (Mäkelä et al. 1999; Weihua et al. 2000) the effects of ER α and ER β antagonize each other (the so-called Yin-Yang theory). Hence, a substance which binds exclusively to the ER β and causes the post-re-

Fig. 15. Computer-assisted tomography was used to determine the degree of osteoporosis developing in rats within 3 months after ovariectomy. In this experiment the trabecular density of the tibia (MT) was measured. Estradiol was able to almost totally prevent osteoporosis while the AC extract had a minor positive effect on the degree of osteoporosis.

* $P < 0.05$ vs pre ovx; # $P < 0.05$ vs 3 months after ovx

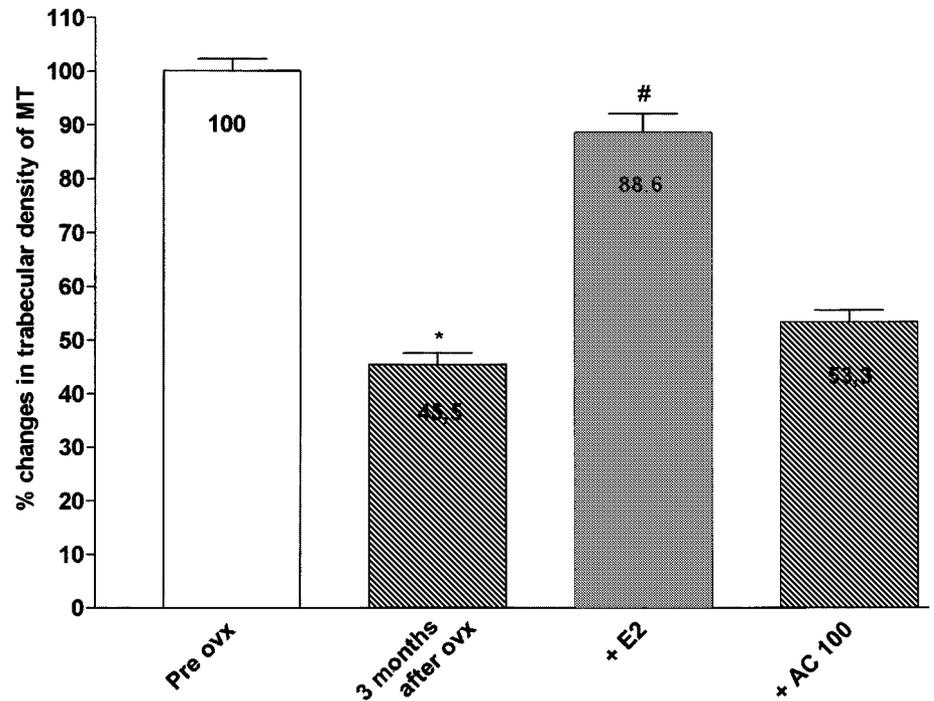
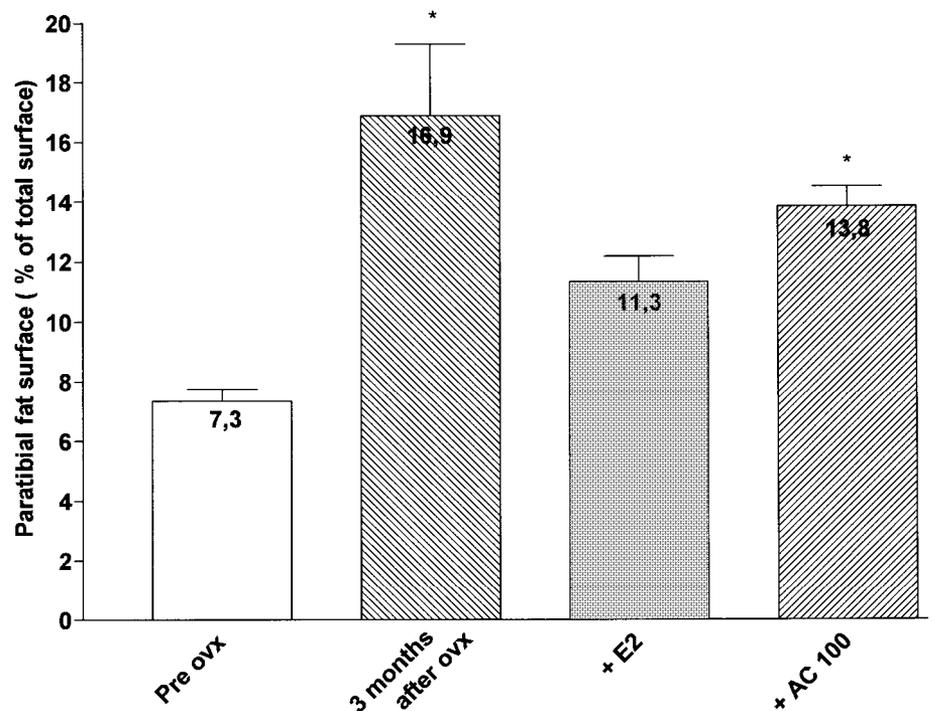


Fig. 16. Computer-assisted tomography allows determination of the size of a paratibial fat depot which is large after 3 months of ovariectomy and significantly smaller prior to ovx and in E2- or AC-treated animals. Hence, the AC extract had a marked effect to prevent ovariectomy-induced fat accumulation.

* $P < 0.05$



ceptor transcriptional activation would be a desirable tool to study the physiology of the ER β and possibly the usefulness of ER β agonists in the treatment of estrogen-dependent tumors. In an attempt to characterize the putative estrogenic substances in the *Vitex agnus castus* BNO1095 extract closer, recombinant estrogen

receptor- α and estrogen receptor- β proteins were utilized. While the estrogenic constituents in the AC extract did not bind to the ER α protein, specific binding, however, was demonstrable for the estrogen receptor of the β -subtype. Recently we identified apigenin, a flavonoid, as the major component with pure agonistic

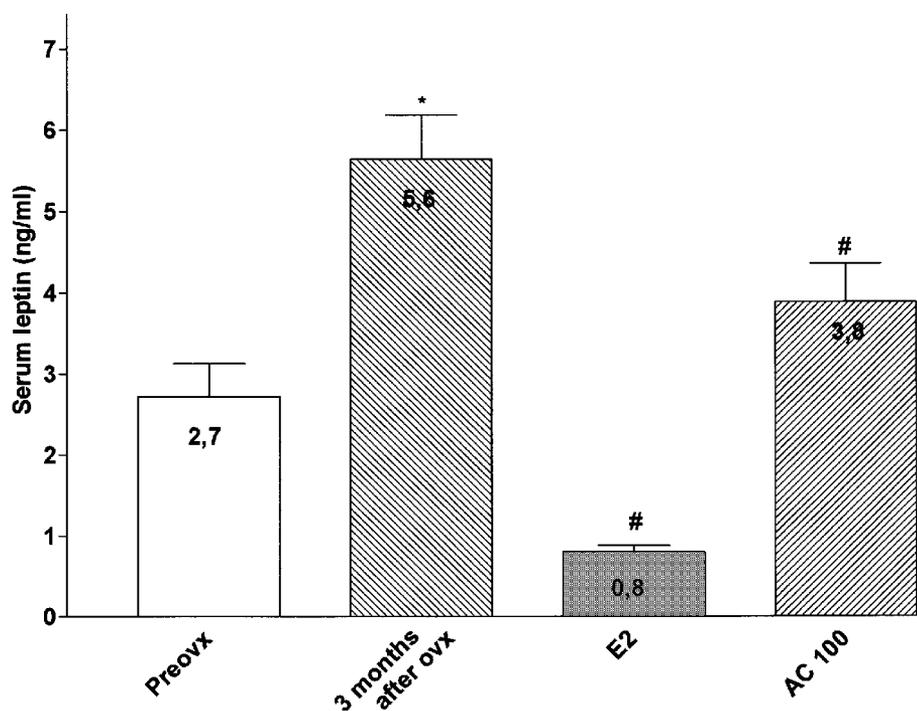


Fig. 17. Leptin is a hormone produced by lipocytes and their concentrations are high in animals ovariectomized for 3 months. Significantly lower leptin concentrations are found in E2- and AC-treated animals. * $p < 0.05$ vs pre ovx; # $p < 0.05$ vs E2 and AC100

activity to the estrogen receptor of the β -subtype. Apigenin is well known as plant constituent but it is the first time that it was identified in *Vitex agnus castus* extracts. In an earlier publication, Kuiper et al. (1998) already demonstrated a high ER β -binding activity of apigenin. Surprisingly, however, although an IC₅₀ for the ER α could not be determined due to too weak binding to the ER α , the transactivating activity of apigenin in ER α -transfected cells was identical of its ER β -transactivating activity (Kuiper et al. 1998). According to the Yin-Yang theory of Gustafsson, ER α and ER β have each other opposing functions. Hence, a pure ER β agonist should have no uterine effect since the uterus expresses primarily ER α . Indeed, we were able to show that *Vitex agnus castus* extracts given acutely (6 h), subacutely (7 days) or chronically (3 months) at 2 different doses had no effects on uterine weight or on the regulation of any of the uterine genes known to be estrogen-controlled. After a 3 months oral application, however, we did observe a slight, statistically not significant osteoporosis-protecting effect (Fig. 15) and a marked estradiol-like effect on a paratibial fat depot utilizing computer-assisted tomography (Fig. 16). As a result of decreased fat accumulation in response to chronic (3 months) estradiol or *Vitex agnus castus* treatment serum leptin (a hormone produced by lipocytes) was also significantly reduced when compared to rats fed with phytoestrogen-free food (Fig. 17). In accordance with the small, insignificant antioestrogenic effect exerted by the ER β -specific *Vitex*

agnus castus extracts, no significant effects were observed on bone activity markers in the serum such as osteocalcin and bone-specific alkaline phosphatase.

In summary, we showed that *Vitex agnus castus* extract BNO 1095 contains dopaminergic substances which suppress pituitary prolactin release one of which was only slightly less potent than dopamine in suppressing prolactin release from cultivated pituitary cells. This substance was chemically identified as a clerodadienol. A commercially available AC preparation tested clinically has been successfully used in patients suffering of premenstrual mastalgia. In addition, the extract contains estrogens with selectivity for the estrogen receptor β -subtype which appears to be involved in the regulation of fat tissue but which exert no estrogenic effects in the uterus and which have little effects in the bone.

Acknowledgements

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