Molecular and Cellular Endocrinology, 78 (1991) 1–6

MOLCEL 02498

Review

Medicinal uses of licorice through the millennia: the good and plenty of it

Elizabeth A. Davis [1] and David J. Morris [2]

[1] *Department of Pathology and Laboratory Medicine, The Miriam Hospital, Providence, RI 02906, U.S.A., and* [2] *The Division of Biology and Medicine, Brown University, Providence, RI, 02912, U.S.A.*

Key words: Licorice; *Glycyrrhiza glabra*; (Review)

Licorice continues to be used as a pharmacological agent as well as an ingredient in tobacco and confectionery throughout countries in the East and West. Studies over the past 50 years have yielded information which has prompted new interest in the pharmacological and physiological effects of this plant. This research has revealed that the chemical structure of one of the principle agents in the root of the licorice plant is a glycoside of a triterpene called glycyrrhetinic acid. Originally its structure and activity were thought to be similar to adrenal steroid hormones such as aldosterone and cortisol, since ingestion of licorice mimicked hyperaldosteronism and was suggested as a treatment for Addison's disease [1,2]. It is now thought that the presence of intact adrenals is required for licorice ingestion to cause sodium retention leading to subsequent hypertension [3]. This recent insight into the effects of licorice on adrenal function and steroid metabolism has led us to examine the uses of licorice historically and culturally in order to arrive at a better understanding of its many possible functions. In realizing how widely licorice has been used in many societies throughout the millenia, not only can we gain insight into its possible medicinal functions, but we can also learn to what extent licorice may pose as a potential threat to the individual. Furthermore, it is fascinating to account for some of its uses in the past in view of our present knowledge of its biochemical structure and physiological effects.

The licorice with which we are familiar in the Western part of the world comes from the plant *Glycyrrhiza glabra*. The plant is indigenous to Greece, Turkey, Spain, Iraq, Caucasian and Transcaspian Russia, and northern China [4]. According to Lucas in his book entitled *Nature's Medicines* [4], the earliest evidence we have of the employment of licorice comes from the stores of licorice found in the ancient tombs of Egyptian pharaohs, including that found in the 3000-year-old tomb of King Tut. Lucas claims that this was an Egyptian ritual which allowed the spirits of the kings to prepare a sweet drink called *mai sus* in the afterlife. An iced drink, *Mai sus*, is still consumed today by the Egyptians and is made available by 'itinerant venders' [4,5]. References to licorice have also been made on Assyrian tablets dating back to the second or third millenia B.C. [5].

Other accounts date back to ancient Greece and Rome where licorice was commonly used as a tonic and cold remedy, as well as for other purposes less familiar to us. In the fourth century B.C., the Greek botanist and contemporary of Aristotle, Theophrastus (ca. 370–288/5 B.C.), refers to licorice as 'Scythian root' or 'sweet root' in his *Enquiry into Plants* [6]. This ancient herbalist, also interested in the history of licorice, claims that the Scythians, whose civilization was established early in the first millennium B.C., used

Address for correspondence: D.J. Morris, The Miriam Hospital, Dept. of Laboratory Medicine, 164 Summit Avenue, Providence, RI 02906, U.S.A. Fax: 401-331-8500 ext. 4534.

licorice and mare's milk cheese and could subsequently abstain from drinking for 11 or 12 days [6]. Theophrastus also mentions that licorice is useful in treating asthma, and when administered in honey, the root heals wounds [6].

In the first century B.C., Pliny the Elder also makes mention of the various functions of licorice root. Pliny alleges that licorice in the form of a lozenge clears the voice and postpones hunger and thirst [7,8]. He agrees with Theophrastus, suggesting that cheese 'made of mare's milk and licorice' in 'small quantities' will assuage these symptoms of hunger and thirst [7]. Furthermore, according to Pliny, the root of the licorice plant was appropriately referred to as *adipsos* [8] by the ancients, a word which can be translated as 'not suffering from or causing thirst'. Pliny states that, because of its association with thirst, licorice has served as a remedy for patients suffering from dropsy. He continues, 'it is for this reason, too ... that the powder of it is often sprinkled on ulcerous sores of the mouth and films on the eyes; it heals, too, excrescences of the bladder, pains in the kidneys, condylomata, and ulcerous sores of the genitals.' [8,9].

As reported by Lucas in *Nature's Medicines* [4], the ancient Hindus believed that licorice increased sexual vigor, and they prepared the concoction as a beverage, mixing the licorice with milk and sugar. The ancient Chinese thought that licorice root gave them strength and endurance, and they prepared it most often in tea for medicinal purposes. According to W.T. Fernie in his *Herbal Simples* (1897), the Chinese found that the licorice root from *Glycyrrhiza echinata* and *Glycyrrhiza glabra* contains 'tonic, alterative (bringing about slow gradual change) and expectorant properties' and the root serves as 'a mild aperient'; Fernie also indicates that the Chinese ascribe rejuvenating and nutritive qualities to it [10].

Early popular books on herbal medicines, both English and American, provide some of the most thorough accounts of Western uses of *Glycyrrhiza glabra*. *Glycyrrhiza glabra*, having been native to warmer European countries, is recorded as having been cultivated in England for the first time in 1562. Fernie, unlike his predecessors, presents a description of the competition of the licorice root: a sugar called glycyrrhizine (a demulcent starch), asparagin, phosphate and malate of lime and magnesia, albumen, and woody fibre. Fernie regrets to say that 'liquorice is commonly aldulterated with potato starch, miller's sweepings mixed with sugar, and any kind of rubbish' [10]. He suggests that the sugar of licorice is safe for diabetics and claims that licorice in porter and stout supposedly both adds sweeteness, thickeness, and blackness to drinks and simultaneously prevents their fermenting. Fernie also mentions the employment of black licorice in tobacco, both chewing and smoking.

Nicholas Culpepper [11], one of the most popular and enduring English herbalists of the seventeenth and eighteenth centuries, as well as the early nineteenth century American herbalists, Samuel Stearns [12] and John Monroe [13], give almost identical accounts of the pharmacological attributes of the licorice root. They assert, as do other herbalists and historians, that the root serves as an emollient, demulcent, attenuant, expectorant, detergent, and a diuretic. The root 'abates thirst in dropsies', 'helps defluctions of the breast', 'softens acrimonious humours', 'temperates salt', 'allays the heat of the blood', promotes urine, and thickens the sanguinary fluid, when too thin'. Moreover, the root is 'good for pleurisy, gravel, dysury, and intense pain'.

Earlier accounts by William Langham [14] and Robert Lovell [15] reveal that as far back as the early seventeenth century licorice was believed to alleviate sickness and pain when administered in combinations with other food. Most interesting are their recipes for internal sores and ulcers, including the 'running of sores' inside the ears; Lovell, in rather vague terms, claims that licorice root, when applied (perhaps as an ointment), remedies 'green wounds'. Furthermore, a licorice bread is said to assuage the 'heat of stomach and mouth', a consequence of thirst and dehydration [15].

Glycyrrhiza glabra was probably introduced to the Native Americans by early English settlers [4] and consequently adopted into their traditional pharmacopoeia. Diabetes, which affects at least 25% of the adult population, has been commonly treated with *Glycyrrhiza* or a similarly sweet herb called *Cirsium ochrocentrum*. The medicine man will prescribe licorice to 'keep sugar down', a practice which demonstrates that the inherent sweetness of licorice is thought to reflect the plant's

medicinal function to treat diseases caused by high sugar levels [16].

As in the Western cultures previously described, *Glycyrrhiza glabra* continues to be employed by non-Western cultures for treatment of similar ailments. In India licorice is believed to ease thirst in an antitussive and a demulcent, and it serves as a treatment for influenza, uterine complaints, and biliousness [17]. The Chinese and their Far Eastern neighbors have traditionally used licorice most extensively. While the typical European licorice, or 'Spanish licorice' as it is sometimes called, comes from the plant *Glycyrrhiza glabra*, the licorice used in the Far East comes from the plant *Glycyrrhiza uralensis*. Indigenous to Northern China, Mongolia, and Siberia, it is referred to as 'gan cao' (or 'kan ts'ao') by the Chinese [18,19]. The root is considered to benefit all organs of the body. The general composition of *Glycyrrhiza uralensis* includes 6–14% glycerrhizin, glycyrramarin, liquiritin, iso-liquiritin, mannitol, glucose, sucrose, and starch [19].

In modern Chinese medicine, many medicinal remedies contain licorice as an ingredient. Extracts of licorice root are distributed easily within the body, where it is broken down and absorbed slowly [20,21]. Chinese herbal medicine instructs that again *Glycyrrhiza uralensis* be employed as a tonic, an antipyretic, an antidote (e.g. counteracting mushroom poisoning), a demulcent to the lungs, an expectorant, an analgesic, to soothe sore throats and coughs, to treat asthma, and to alleviate toxic abscesses as well as acute abdominal pains. In addition, *Glycyrrhiza uralensis* is used in Chinese recipes for food treating acne and pimples, frost bite, heat stroke, and nervous disorders such as hysteria, irritability, epilepsy, manic depression, violent temper, etc., and curiously, hypertension. It should be noted that while licorice is used in recipes which treat symptoms of hypertension related to nervous disorders and stress, licorice is not present specifically in the recipe for high-blood pressure that is discussed in *Chinese Herbal Medicine* by Reid [19].

Licorice continues to serve as a flavoring agent, sweetening the bitter taste of many drugs, as a filler for pills, and as an 'essential ingredient in ointments for treating skin diseases'. Licorice also slows and prolongs the effects of strong tonic medicines. Because the Chinese recognize the capacity of licorice to imitate the activity of adrenocortical hormones, they use licorice to treat Addison's disease [18]. Most common is the employment of licorice 'as an emollient for duodenal and peptic ulcers'. Until approximately ten years ago when cimetidine was marketed, licorice was a primary antipeptic ulcer drug [20]. Licorice extract is also used as a flavoring agent in soy sauce in both China and Japan.

Very large quantities of *Glycyrrhiza glabra*, both root and extract (greater than 40,000,000 lbs. per year were reported for 1952 [4]), are imported to the U.S.A. from Iraq, Turkey, Russia, Syria, Italy, Spain, and East Africa. The largest portion of licorice extract imported to the United States is employed by tobacco industries as a conditioning and flavoring agent [4,5]. Because licorice cures tobacco, it has been used for approximately 100 years in cigars, pipe tobacco, cigarettes, and chewing tobacco, and is even present in snuff [5,22]. We are most familiar with the role of licorice in the confectionery industry in Western countries where varieties of licorice candies are prepared by a simple process. Licorice is extracted from the root with water and vacuum concentrated. It is from this 'block juice' that all licorice candies are made. Once licorice juice is combined with sugar, corn syrup, and flour, it forms a paste which can be moulded into any desirable shape. However, many licorice candies in the United States now contain anethole, a major constituent in the aniseed plant, as a substitute flavoring agent for licorice.

Aside from its universal role as an expectorant and demulcent in many familiar over-the-counter remedies, licorice root has been featured in powdered form as a filler for pills in the U.S.A. as well, both enhancing the consistency of the pill and coating the surface. Some commercial hand, body, and skin lotions contain licorice as an ingredient. Furthermore, it is also used in ointments as a remedy for various skin disorders since glucocorticoid action is potentiated by either glycyrrhizin or glycyrrhetinic acid [5,23]. Other possible pharmacological actions of licorice have been evaluated by the early work performed by Costello and Lynn [24] in 1949 who extracted estrogenic constituents from *Glycyrrhiza glabra*; they sug-

gested that this plant might be a source of low-cost estrogens to be used for medicinal purposes in treating hormone imbalances associated with menstruation. However, in contrast, the glycoside of glycyrrhetinic acid has also been shown to possess anti-estrogenic activity, inhibiting the effect of estradiol on uterine growth in ovariectomized animals [25]. Since 1906, licorice extract residues have been used successfully to extinguish fires in a fire-foam suspension [5]. For similar reasons, licorice as an emulsifier has been used in the United Kingdom to create foam in drinks and alcoholic beverages [4,5]. Licorice by-products have also been used as an excellent compost medium for mushrooms, the reasons for which still remain unknown [4,5].

Beginning in the late 1940s and extending well into the 1950s, there was a growing interest in the metabolic activity of glycyrrhetinic acid. Investigations into various side-effects of licorice treatment of adrenal and electrolyte disorders, such as Addison's disease, peptic ulcers and rheumatoid arthritis, showed that licorice can produce a syndrome mimicking hyperaldosteronism, which may lead to subsequent hypertension.

As mentioned before, licorice extracts have been commonly used and still continue to be used in many European countries to relieve gastric and duodenal ulcers, supposedly as an inhibitor of gastric secretion. The anti-peptic ulcer drug carboxolone sodium, developed in the early 1960s by a team from Biorex Laboratories, London, headed by Dr. S. Gottfried and L. Baxendale, is a succinate derivative of glycyrrhetinic acid which is the major chemical triterpenoid constituent in licorice [26]. This drug evolved from the widespread usage of licorice in Holland and other European countries throughout the Middle Ages and earlier for the treatment of peptic ulcers. Save for the United States, which was concerned with the possible blood-pressure elevating properties of the drug, carbenoxolone sodium has been extensively employed for the purpose of alleviating ulcers throughout the world.

Interestingly, as early as 1948, Revers [27] reported his observations that approximately one out of five patients who were treated with licorice paste for peptic ulcers developed edema. Molhuysen et al. (1950) also noticed the side-effects associated with the use of licorice which generally resulted in the retention of water, sodium, and chloride, and were accompanied by increased excretion of potassium [28]. They also concluded that licorice extracts exhibit effects similar to that of large injections of deoxycorticosterone (DOC), but the effects are more persistent, even after the drug has been discontinued until a salt-free diet is given. However, they did not observe a positive response, but rather a slight negative response, to licorice extract in a patient suffering from Addison's disease who did not respond to ACTH. These observations inspired Card et al. (1953) to examine further the effects of licorice on normal subjects as well as on patients who suffered from Addison's disease, and to investigate the DOC-like activity of licorice [29]. Their results differed from those of the previous examiners, and they concluded that licorice appeared to have positive results in reversing the effects of Addison's disease.

In 1957, Kumagai et al. [30] were encouraged by the observations made by Molhuysen et al. [28] concerning the effect of licorice extract on rheumatoid arthritis. They established in their report that when glycyrrhizine is administered along with ACTH or cortisone, favorable effects of glycyrrhizine on rheumatoid arthritis are achieved. Without the concomitant use of glucocorticoids or equivalents such as cortisone or ACTH, respectively, licorice has little effect on acute rheumatic episodes or electrolyte balance. The product of these and other investigations culminated in the realization that an intact adrenal gland was required for many of the effects of licorice; the demonstration that carbenoxolone and glycyrrhetinic acid can themselves bind to mineralocorticoid receptors at very high levels [31,32] suggests that such doses are rarely achieved therapeutically, and that the main effect of licorice is to potentiate rather than mimic endogenous steroids.

There has been a variety of other studies on the pharmacological effects of licorice. Yamamoto et al. [33], for example, discovered that glycyrrhizin promotes the biosynthesis of cholesterol in rat liver. The excretion of cholesterol in the liver appears to be proportional to a subsequent decrease of cholesterol levels in the blood. These findings are cited by H. Wagner and P. Wolff [33].

Morris, Davis, and Latif [34], and Guthrie et al. [35] have recently demonstrated the potential dangers of licorice used as a flavoring agent in many brands of chewing tobacco in the United States. Because glycoside derivatives of glycyrrhetinic acid induce symptoms of mineralocorticoid excess through the inhibition of 11β-hydroxysteroid dehydrogenase (11β-OHSD), the continual use of chewing tobacco can result in hypertension, sodium retention, and hypokalemia. In their report, Morris et al. [34] claim that glycyrrhetinic acid present as its glycoside in chewing tobacco inhibits hepatic $\Delta^{4,5}$-β-steroid-reductase in addition to 11β-OHSD, thereby preventing the reduction of the A ring of steroids, a major metabolic pathway for the inactivation of both glucocorticoids and mineralocorticoids.

Hypertensive children with the syndrome of apparent mineralocorticoid excess (AME) lack 11β-hydroxysteroid dehydrogenase (11β-OHSD) enzyme activity, a condition resulting in reduced peripheral metabolism of cortisol. Stewart and Edwards et al. [3,36] realized that licorice ingestion causes biological consequences and changes in the pathways of adrenal steroid metabolism similar to those demonstrated by Ulick, New and co-workers [37–39] in these children with the syndrome of AME. Glycyrrhetinic acid, present as its glycoside in licorice has been shown to be a potent competitive inhibitor of 11β-OHSD [39]. Their experiments together with those of Funder et al. suggest [37–40] that lowered 11β-OHSD activity results in higher peripheral and intrarenal concentrations of corticosterone in experimental animals and cortisol in humans, which may then interact with mineralocorticoid (MC) receptors and promote Na^+ reabsorption.

However, other processes may also be involved. Souness and Morris [41] reported that indeed acute pretreatment of adrenalectomized male rats with carbenoxolone sodium, the water-soluble succinate derivative of glycyrrhetinic acid, caused both cortisol and corticosterone to display significant mineralocorticoid-like activity, particularly Na^+ retention. They also showed that the same dosage of carbenoxolone sodium, which does not affect Na^+ or K^+ excretion on its own, amplifies the antinatriuretic but not the kaliuretic activity of the two mineralocorticoids, aldosterone and 11-deoxycorticosterone [40]. The latter steroid is particularly significant since it does not possess a hydroxyl group at the c-11 position in the steroid nucleus and therefore is not a substrate for the enzyme 11β-OHSD. Glycyrrhetinic acid has also been shown by Latif et al. [43] to be a potent inhibitor of the important steroid metabolizing enzyme, 5β-reductase and also as an inhibitor of 3β-hydroxysteroid dehydrogenase, to a lesser extent. It does not inhibit 5α-reductase. Thus licorice derivatives reroute the metabolism of aldosterone, deoxycorticosterone, and glucocorticoids resulting in the accumulation of unmetabolized hormones and their corresponding 5α-dihydro and 3α,5α-tetrahydro derivatives (as in children with the syndrome of AME).

Thus after almost half a century, it is no wonder that there has been a resurgence of interest in licorice, since many of the properties ascribed to this plant by several cultures throughout history now need to be re-examined in another light. Who knows what new insight into a host of medicinal cures and clinical problems may once more be focussed around extracts of *Glycyrrhiza glabra*.

Acknowledgements

The authors thank Dr. M. Sheff, the Miriam Hospital, and Dr. A. Brem for helpful discussions concerning the work.

References

[1] Borst, J.G.G., Ten Holt, S.P., De Vries, L.A. and Moluyson, J.A. (1953) Lancet ii, 657.
[2] Conn, J.W., Rovner, D.R. and Cohen, E.L. (1968) J. Am. Med. Assoc. 205, 80–84.
[3] Stewart, P.M., Wallace, A.M., Valentino, R., Burt, D., Shackleton, C.H.L. and Edwards, C.R.W. (1987) Lancet ii, 821–823.
[4] Lucas, (1976) in Nature's Medicines, pp. 89–94, Melvin Powers/Wilshire Book Company, No. Hollywood, CA.
[5] Houseman, P.A. (1944) in Licorice — Putting a Weed to Work, pp. 3, 10–15, The Royal Institute of Chemistry of Great Britain and Ireland, London.
[6] Theophrastus (1916) in Enquiry into Plants and Minor Works on Odours and Weather Signs (transl. by Sir Arthur Hort), Book IX, Chapt. 8, Par. 2, William Heinemann, London/G.P. Putnam's Sons, New York.
[7] Pliny (1856) in The Natural History (transl. by John Bostock and H.T. Riley), Book XI, Chapt. 119, Henry G. Bohn, London.

[8] ibid., Book XXII, Chapt. 11.
[9] ibid, Book XXVIII, Chapt. 27.
[10] Fernie, W.T. (1897) in Herbal Simples, Boericke and Tafel, Philadelphia, PA.
[11] Culpepper, N. (1800) in English Physician Enlarged, pp. 173-174, printed for J. Scratcherd, Ave-Maria-Lane; J. Walker, Paternoster-Row; W. Lowndes, Fleet St.; and J. Barker, Great Russell St., Covent Garden, London.
[12] Stearns, S. (1801) in The American Herbal or Materia Medica, printed by David Carlisle, Walpole, for Thomas and Thomas, and the Author.
[13] Monroe, J. (1824) in The American Botanist, and Family Physican, pp. 65–66, Jonathan Morrison, Wheelock, VT.
[14] Langham, W. (1633) in The Garden of Health, printed by Thomas Harper, London, with permission of the Company of Stationers.
[15] Lovell, R. (1659) in A Compleat Herball, printed by William Hall, Oxford, for R.I.C. Davis.
[16] Camazine, S. (1986) in Folk Medicine (Steiner, R.P., ed.), pp. 23–38, American Chemical Society, Washington, DC.
[17] Patel, N.G. (1986) in Folk Medicine (Steiner, R.P., ed.), pp. 41–65, American Chemical Society, Washington, DC.
[18] Li, C.P. (1974) in Chinese Herbal Medicine, pp. 67–68, John E. Fogarty International Center for Advanced Study in the Health Sciences, Bethesda, MD.
[19] Reid, D.P. (1987) in Chinese Herbal Medicine, pp. 28–36, 143, 146, 160–162, Shambhala Publications, Boston, MA.
[20] Cha, S. (1990) Providence, RI Brown University, (personal communication).
[21] A Trip Report of the American Herbal Pharmacology Delegation (197–?) Herbal Pharmacology in the People's Republic of China, pp. 156–157, National Academy of Sciences, Washington, DC.
[22] Bell, J.H. (1980) Tobacco Sci. 24, 126–129.
[23] Wagner, W., Bladt, S. and Zgainski, E.M. (1984) in Plant Drug Analysis, Springer-Verlag, Berlin, Heidelberg, New York, Tokyo.
[24] Costello, C.H. and Lynn, E.V. (1949) J. Am. Pharm. Assoc. 6, 177–180.
[25] Kumagai, A., Nishino, K., Shimomura, A., Kin, T. and Yamura, Y. (1967) Endocrinol. Jpn. 14, 34–38.
[26] Khan, M.H. and Sullivan, F.M. (1967) A Symposium on Carbenoxolone Sodium (J.M. Robson and F.M. Sullivan, eds.), p. 5, Butterworths, London.
[27] Revers, F.E. (1946) Ned. Tijdschr. Geneesk. 90, 135–137.
[28] Molhuysen, J.A., Gerbrandy, J., De Vries, L.A., De Jong, J.C., Lenstra, J.B., Turner, K.P. and Borst, J.G.G. (1950) Lancet ii, 381.
[29] Card, W.I., Mitchell, W., Strong, J.A., Taylor, N.R.W., Tompsett, S.L. and Wilson, J.M.G. (1953) Lancet ii, 663.
[30] Kumagai, A., Yano, S., Otomo, M. and Takeuchi, K. (1957) Endocrinol. Jpn. 4, 17.
[31] Ulmann, A., Menard, J. and Corvol, P. (1975) Endocrinology 97, 46–51.
[32] Armanini, D., Karbowiak, I., Krozowski, Z., Funder, J.W. and Adam, W.R. (198?) Endocrinology 111, 1683–1686.
[33] Wagner, H. and Wolff, P. (1977) in New Natural Products and Plant Drugs with Pharmacological, Biological or Therapeutical Activity, pp. 178–181, Springer-Verlag, Berlin – Heidelberg – New York.
[34] Morris, D.J., Davis, E. and Latif, S.A. (1990) New Engl. J. Med. 322, 849.
[35] Westman, E.C. and Guthrie, G.P. (1990) New Engl. J. Med. 322, 850.
[36] Edwards, C.R.W., Stewart, P.M., Burt, D., Brett, L., McIntyre, M.A., Sutanto, W.S., DeKloet, E.R. and Monder, C. (1988) Lancet ii, 986–989.
[37] Ulick, S., Levine, L.S., Gunczler, P., Zanconato, G., Ramirez, L.C., Rauh, W., Rosler, A., Bradlow, H.L. and New, M.I. (1979) J. Clin. Endocrinol. Metab. 49, 757–764.
[38] New, M.I., Oberfield, S.E., Carey, E., Greig, F., Ulick, S. and Levine, L.S. (1982) in Endocrinology of Hypertension (F. Mantero, C. Biglieri and C.R.W. Edwards, eds.), pp. 85–101, Academic Press, New York.
[39] Monder, C., Stewart, P.M., Lakshmi, V., Valentino, R., Burt, D. and Edwards, C.R.W. (1989) Endocrinology 125, 1046–1053.
[40] Funder, J.W., Pearce, P.T., Smith, R. and Smith, A.I. (1988) Science 242, 583–585.
[41] Souness, G.W. and Morris, D.J. (1989) Endocrinology 124, 1588–1590.
[42] Morris, D.J. and Souness, G.W. (1990) Am. J. Physiol. 258, F756–F759.
[43] Latif, S.A., Conca, T.J. and Morris, D.J. (1990) Steroids 55, 52–58.