Deficiency or excess of vitamin A or retinol is frequent in humans. Severe vitamin A deficiency can be observed in most developing countries (Mora et al., 1998) and affects mainly children and pregnant women, whose needs for retinol are great (Gerster, 1997). In the industrialized countries, severe hypovitaminosis A is rarely found, but an insufficient nutritional intake of vitamin A has been reported in 20–25% of adult women in a study of the Paris region (Hercberg et al., 1994). Conversely, hyper-retinoidaemia is frequently provoked for therapeutic purposes, as high doses of retinoids are used to treat skin diseases and several types of cancer, including cancers of the lung, kidney, skin and blood cells (Dragnev et al., 2000). Oral retinoids such as tretinoin, isotretinoin or etretinate, designed to treat skin diseases such as severe acne and psoriasis, were available between the early 1980s and 1990s and the compliance of pregnancy avoidance policies after the end of treatments with these drugs has not always been respected. The first children born to women treated with these synthetic retinoids are reaching reproductive age but, as yet, no studies have been performed to investigate the effects of these treatments, which greatly increased the concentrations of retinoids sometimes for several months after the end of the treatment, on the fertility of this generation.

A normal diet should provide sufficient dietary vitamin A through the consumption of animal fat, eggs, butter and coloured fruit and vegetables containing beta-carotenes. Moreover, other products such as milk and cereals are artificially supplemented with vitamin A. The use of multivitamin supplements, particularly by women, is also common in the industrialized countries. These cumulative vitamin A intakes may increase retinol above recommended concentrations in subclasses of the population.

Although no study has yet been conducted to evaluate the importance of an alteration in vitamin A and retinoid intake in the development and maintenance of testicular functions in men, it has long been known that retinolaemia in rats and mice is involved in testicular functions but has no effect on ovarian functions. An excess of vitamin A causes testicular lesions and spermatogenetic disorders (Lamano Carvalho et al., 1978). However, vitamin A deficiency induces early cessation of spermatogenesis (Wolbach and Howe, 1925), characterized by degeneration of all the meiotic germ cells (Thompson et al., 1964; Morales and Griswold, 1987) and defective secretion of testosterone (Appling and Chytil, 1981), and can be compensated for by dietary vitamin A supplementation or injection of high doses of retinoic acid, the active metabolite of vitamin A (Thompson et al., 1964; Appling and Chytil, 1981; Van Pelt and de Rooij, 1991). Recent studies have shown that retinoids already affect these three types of cell in fetuses. Curiously, the effects of retinoids on fetal and adult testis seem opposed.

Over the last 10 years, many studies have improved our knowledge of the location of retinoic acid receptors, the identification of their target genes and the involvement of retinoids in testicular development. The aim of this review is to present a synthesis of current knowledge on this question.

Retinoid acid receptors

Retinoic acid receptors belong to the superfamily of nuclear receptors of steroid and thyroid hormones, and include two
Table 1. Localization of retinoic acid receptors (RARs) and retinoid X receptors (RXRs) in fetal, neonatal and adult testis

<table>
<thead>
<tr>
<th></th>
<th>Fetal tests</th>
<th>Neonatal tests</th>
<th>Adult testis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sertoli cells</td>
<td>RARβ; RARγ; RXRγ</td>
<td>RARα; RARβ; RARγ; RXRα; RXRγ</td>
<td>RARγ; RARβ; RARγ; RXRα; RXRγ γ2,4,5,6</td>
</tr>
<tr>
<td>Germ cells</td>
<td>RARα2,3; RARβ2,3; RXRα; RXRβ</td>
<td>RARα2,3; RARβ2,3; RXRα; RXRβ</td>
<td></td>
</tr>
<tr>
<td>Leydig cells</td>
<td>RARα2,3; RARα2,3; RXRα; RXRβ</td>
<td>RARα2,3; RARβ2,3; RXRα; RXRβ</td>
<td>RARα2,3; RARα2,3; RXRβ; RXRγ2,4,5</td>
</tr>
</tbody>
</table>

Receptors the knockout of which induces sterility of testicular origin are shown in bold.

References: 1 Akmal et al., 1997; 2 Boulogne et al., 1999; 3 Cupp et al., 1999; 4 Dufour et al., 1999; 5 Gaemers et al., 1998; 6 Kastner et al., 1996.

main families: retinoic acid receptors (RARs) that bind all-trans and 9-cis retinoic acid isomers, and retinoid X receptors (RXRs) that preferentially bind the 9-cis isomer and activate the transcription of target genes. RXR can interact with the RAR or with other nuclear receptors to act specifically on the retinoic acid response elements and activate the transcription of target genes. RXR can homodimerize or heterodimerize with other transcription factors to bind specific DNA response elements.

The six classes of receptor have been located in rats and mice by immunohistochemistry or in situ hybridization in the different types of cell of the fetal, immature and adult testis (Huang et al., 1994; Kastner et al., 1996; Akmal et al., 1997; Gaemers et al., 1998a; Boulogne et al., 1999; Cupp et al., 1999; Dufour and Kim, 1999).

In the fetal or neonatal testis (Table 1), the gonocytes express the three RAR classes (α, β and γ), as well as the RXR-α and -γ classes, but this expression changes throughout development and the location of the receptors is often cytoplasmic (Boulogne et al., 1999; Cupp et al., 1999). Immature Sertoli cells, which unlike adult Sertoli cells are mitotically active, express only RAR-β and -γ and RXR-α and -γ (Boulogne et al., 1999); however, Dufour and Kim (1999) showed that immature Sertoli cells express RXR-α and -γ and also RAR-α and -β but no RAR-γ. This discrepancy may have occurred because of the use of different antibodies. Fetal Leydig cells, which form a generation of cells distinct from adult Leydig cells, express all three classes of RAR (Boulogne et al., 1999; Cupp et al., 1999) and all three classes of RXR (Boulogne et al., 1999).

In the adult testis (Table 1), four classes of receptor have been identified in the germ cells: RAR-α and -β and RXR-α and -γ (Kastner et al., 1996; Akmal et al., 1997; Gaemers et al., 1998a; Dufour and Kim, 1999). RAR-α is expressed essentially from the spermatocyte to the spermatid stage in the course of elongation, whereas RXR-β is expressed earlier, from the spermatogonia to the round spermatid stage. RXR-α and -γ are expressed at all these stages. The haploid germ cells no longer express any retinoic acid receptor from the elongated spermatid stage onwards. The adult Sertoli cells express all six classes of retinoic acid receptor, and the Leydig cells express all classes except RAR-α (Akmal et al., 1997).

Thus, the distribution of retinoic acid receptors in the testis is very complex and often redundant, and depends not only on the type of cell but also on the stage of testicular differentiation and the spermatogenic stage. In addition, these receptors are sometimes located in the cytoplasm and are therefore inactive (Boulogne et al., 1999; Dufour and Kim, 1999). The receptors may be transported into the nucleus in the presence of retinoic acid or according to other signals (Akmal et al., 1997). Thus, for example, in the Sertoli cells, the nuclear location of RAR-α can be induced by retinoic acid and blocked by the action of FSH (Braun et al., 2000). Similarly, the expression of retinoic acid nuclear receptors is not constant and may be subject to different types of regulation. In particular, in the testis of vitamin A-deficient animals, retinol increased the expression of RAR-α mRNA (Kim and Griswold, 1990; Akmal et al., 1998) without changing the concentration of RXR-β mRNA (Kim and Griswold, 1990). Retinoic acid increases the expression of RAR-β (Gaemers et al., 1997). These findings imply a complex model of signalling. However, only mice mutant for RAR-α or for RXR-β were rendered sterile by defective testicular functions (Lufkin et al., 1993; Kastner et al., 1996), indicating that these are probably the two most essential receptors.

Finally, the transcriptional activity of retinoic acid nuclear receptors may be modulated by interaction with other proteins acting as co-activators or co-repressors. These factors appear to act by modifying the acetylation of DNA histones, thus modifying the structure of chromatin and thereby preventing transcription. Many of the co-activators have histone acetyl transferase activity, whereas co-repressors either have histone deacetylase activity or are associated with other proteins that have histone deacetylase activity. In the absence of a ligand, the heterodimer RAR–RXR might be associated with a co-repressor such as the silencing mediator for retinoic acid and thyroid hormone receptors or the nuclear receptor co-repressor (Bernardini et al., 1997; Leo et al., 2001). Receptor activation...
by retinoic acid may dissociate the co-repressor complex and induce the recruitment of co-activators such as the steroid receptor co-activator 1, receptor-associated coactivator, cellular retinol-binding protein (CRBP) or thyroid hormone receptor-interacting protein (Bernardini et al., 1997; Leo et al., 2001). There may be a third category of coregulators acting as repressors on receptors bound to their ligand, as is the case for the receptor-interacting protein (Wei et al., 2001). Unfortunately, in the testis, the expression of all these co-activators and co-repressors and their interaction with retinoid receptors is poorly documented.

**Metabolism of retinol in the testis**

It was thought that retinol exerts action in the testis but that retinoic acid exerts none (Thompson et al., 1964). Injection of physiological doses of retinol, and not of retinoic acid, does restore normal spermatogenesis in vitamin A-deficient rats. However, Van Pelt and de Rooij (1991) showed that
spematogenesis can be re-initiated by retinoic acid, provided that it is injected repeatedly at very high doses, indicating that the blood–testis barrier inhibits the passage of retinoic acid circulating towards the germ cells, and that the Sertoli cells synthesize retinoic acid from circulating retinol. This contention is supported by the fact that the passage of radioactive retinoic acid into the testis is inhibited compared with the passage of retinoic acid into other tissues (Kurlandsky et al., 1995).

It is now known that the stages of the testicular retinoid metabolism are complex and involve different types of cell (Fig. 1). The first step in this metabolism takes place in the peritubular cells, which contain large quantities of CRBP, an intracellular protein that binds retinol with a high affinity (Blaner et al., 1987). The peritubular cells take up the circulatory retinol bound to other transport proteins, such as retinol binding protein (RBP) and transthyretin (TTR), and secrete it as a complex formed with a new RBP, in the direction of the Sertoli cells (Davis and Ong, 1995).

CRBP is also present in Sertoli cells and its expression varies according to the stage of the cycle of the seminiferous epithelium, indicating that the need for retinol depends on the type of germ cells present (Blaner et al., 1987; Schmitt and Ong, 1993). Sertoli cells are the main site of retinoid acid synthesis (Cavazzini et al., 1996). Thus, the enzymes allowing retinol oxidation into retinoic acid (alcohol dehydrogenase and retinal dehydrogenase) are essentially located in the Sertoli cells (Deltour et al., 1997; Zhai et al., 2001). These cells may then ‘distribute’ the retinoic acid to their neighbours, notably to germ cells. Furthermore, production of retinoic acid by Sertoli cells increases during testicular development. Sertoli cells are also the main site of retinol storage. They express lecithin–retinol acyltransferase (LRAT), which allows the esterification of retinol (Cavazzini et al., 1996). FSH and retinoic acid increase retinol storage in the form of retinyl esters in Sertoli cells but retinol oxidation to retinoic acid is reduced by retinoic acid and increased by FSH (Guo et al., 2001). However, the germ cells may themselves store retinol in the form of retinyl ester, because they also express LRAT, especially at the spermatid stage (Schmitt and Ong, 1993), and may also synthesize their own retinoic acid.

Leydig cells also express the enzymes necessary to convert retinol into retinoic acid (alcohol dehydrogenase (ADH) and retinal dehydrogenase) (Deltour et al., 1997; Lopez-Fernandez and del Mazo, 1997; Hardy et al., 2000; Zhai et al., 2001). Several of the enzymes of retinoic acid metabolism may actually be using androgens as substrates in the testis (Hardy et al., 2000).

Also present in the testis are cellular retinoic acid binding protein types I and II (CRABP), which bind retinoic acid to facilitate its transport to the nucleus or its catabolism in the different types of testicular cell, except for the peritubular cells (Blaner et al., 1987; Faraonio et al., 1993; Zheng et al., 1996). However, these proteins do not appear to be essential because animals mutant for the two types of CRABP are normal in their development, fertility, lifespan and general behaviour (Lampron et al., 1995).

**Retinoids and testicular development**

Retinoic acid causes disruption of the seminiferous cords in the testis of rat fetuses (Marinos et al., 1995; Cupp et al., 1999; Livera et al., 2000) (Fig. 2) and also has numerous other effects on testicular development (Table 2). Cupp et al. (1999) showed that retinoids increased transcription of the three isoforms of transforming growth factor β (TGF-β) in cultured neonatal testicular cells.

Our group used an organotypic culture system to show that retinoic acid inhibits the stimulatory effect of FSH on the production of cAMP in rat Sertoli cells during fetal and neonatal life. The use of selective synthetic analogues of the different RAR and RXR revealed that this effect involves RAR-α (Livera et al., 2001). Furthermore, after birth, retinoic acid increases the proliferation of Sertoli cells via RAR-β (Livera et al., 2001) as well as their production of transferrin (G. Livera, unpublished).

Retinoic acid diminishes the proliferation of fetal and neonatal gonocytes by acting on both apoptosis and mitosis via the activation of RAR-α (Boulogne et al., 1999; Livera et al., 2000, 2001; B. Boulogne, unpublished). The knockout of RAR-α led to an increase in the number of germ cells in mouse fetuses and neonates, indicating the involve-

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**Fig. 2.** Effect of retinoic acid (RA) on the organization of the seminiferous cords in testis of rat fetus. A fetal testis was explanted at day 14.5 after conception and cultured for 3 days in the absence or presence of 10⁻⁶ mol retinoic acid l⁻¹. At the time of explantation (14.5 days after conception) and after culture (14.5 + 3.0 days), Sertoli cells were identified by immunolocalization of anti-Müllerian hormone. Scale bar represents 100 μm.
ment of the RAR-α receptor in the control of fetal gameto-
genesis, and implying that, in mice, circulating concentra-
tions of retinoids exert a negative physiological effect on the
onset of the germinal line (G. Livera, unpublished).

In rats, retinoids also reduced basal secretion of testos-
terone in fetal Leydig cells during differentiation of these
cells (Livera et al., 2000). However, in the presence of high
doses of LH or hCG, retinoids stimulated testosterone
secretion (G. Livera, unpublished). The moderate vitamin A
deficit results in increased testicular steroidogenesis during
fetal and neonatal life, showing that circulating concentra-
tions of retinol exert a physiological inhibitory effect on the
development of the endocrine function of the testis in rats
(G. Livera, unpublished).

Retinoids and Sertoli cell functions

Retinoids are involved in the control of numerous functions
in adult Sertoli cells (Table 2), the best documented of
which is Sertoli cell secretion. Retinoids increase the secre-
tion of transferrin, androgen-binding protein (ABP), insulin-
like growth factor-binding protein 4 (IGFBP-4), inhibin α and
glycoproteins, especially sulphated glycoprotein (Sgp-2), but
inhibit the secretion of plasminogen activator and oestrogens
in response to FSH (Rosselli and Skinner, 1992; Galdieri
and Nistico, 1994; Guma and Bernard, 1994; Zhuang et al.,
1997; Gaemers et al., 1998; Zhuang et al., 1997; Canipari and
Galdieri, 2000; Samy et al., 2000; Eskild et al., 1988; Kim and
Griswold, 1990; Gaemers et al., 1997; Gaemers et al., 1998;
Huang and Marshall, 1983; Chaudhary et al., 1989; Lee et al.,
1999; Lefevre et al., 1994).

### Table 2. Principal effects of retinoids on testicular cells

<table>
<thead>
<tr>
<th>Testis</th>
<th>Fetal</th>
<th>Neonatal</th>
<th>Adult</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sertoli cells</td>
<td>↓ Organization of cords(^1)-(^3)</td>
<td>↑ Mitosis(^3)</td>
<td>↑ c-jun, c-myb(^6)</td>
</tr>
<tr>
<td></td>
<td>↑ Transferrin(^4)</td>
<td>↑ Transferrin(^4)</td>
<td>↑ Transferrin(^7)-(^8)</td>
</tr>
<tr>
<td></td>
<td>↓ cAMP response to FSH(^3)</td>
<td>↓ cAMP response to FSH(^3)</td>
<td>↓ cAMP response to FSH(^9)</td>
</tr>
<tr>
<td></td>
<td>↑ TGF-β(^1)</td>
<td></td>
<td>↑ Glycoproteins (Sgp-2)(^11)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>↑ ABP; IGFBP-4(^12)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>↑ COX(^13); ornithine decarboxylase(^14)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>↑ Inhibin A(^15)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>↑ Plasminogen activator(^16,17)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>↑ Androgen receptor(^18)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>↑ PGD2-S(^18)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>↑ CRBP(^19), RARα(^20), RARβ(^21)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>↑ PKC(^10)</td>
</tr>
<tr>
<td>Germ cells</td>
<td>↓ Gonocytes(^3)-(^5)</td>
<td>↓ Gonocytes(^3)</td>
<td>↑ Spermatogonia proliferation(^22)</td>
</tr>
<tr>
<td></td>
<td>↑ Mitosis</td>
<td>↑ Spermatid elongation(^21)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>↑ Apoptosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leydig cells</td>
<td>↓ Basal testosterone secretion(^1)</td>
<td>Without relevant effect</td>
<td>↑ Basal testosterone secretion(^24)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>↑ STAR(^25)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>↑ P450C17(^26)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>↓ 3βHSD(^26)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>↓ LHR(^28)</td>
</tr>
</tbody>
</table>

Abbreviations: TGF-β: transforming growth factor β; PKC: calcium-dependent protein kinase; ABP: androgen-binding protein; IGFBP: insulin-like growth factor-binding protein; COX: cytochrome c oxidase; PGD2-S: prostaglandin D2 synthetase; StAR: steroidogenic acute regulatory protein; P450C17: cytochrome P450 17α-hydroxylase–C17-20 lyase; 3βHSD: 3β-hydroxysteroid dehydrogenase; LHR: luteinizing hormone receptor.

Gaemers et al., 1997; Akmal et al., 1998; Samy et al., 2000). Prostaglandin D2 synthetase, which has a high affinity for retinoic acid and retinol, also serves as a retinoid transporter and is strongly expressed in the blood–testis barrier (Samy et al., 2000).

The basement membrane, which is partly secreted by the peritubular cells, may alter the activity of Sertoli cells by modifying the availability of growth factors. Retinoids may affect the synthesis and deposition of extracellular matrix components through the peritubular cells, for instance by altering the synthesis and secretion of laminin and fibronectin (Ricci et al., 1999).

The interactions between retinoids and FSH, the main regulatory hormone in Sertoli cell functions, are complex. Like retinoic acid, FSH stimulates the secretion of transferrin, ABP and inhibin α (De Jong, 1988; Skinner et al., 1989) and the synthesis of retinyl esters (Guo et al., 2001). However, retinoic acid inhibits the transduction pathway of FSH by blocking the production of cAMP as well as all the activities dependent on it, such as aromatase activity and the secretion of tissue-specific plasminogen activator. In return, FSH reduces the expression of RAR-α (Braun et al., 2000).

**Retinoids and spermatogenesis**

In the testes of vitamin A-deficient rats, spermatogenesis was blocked at the A spermatogonia stage (Morales and Griswold, 1987) and retinoid supplementation retriggered spermatogenesis, which occurred concomitantly in all the tubules (Morales and Griswold, 1987). In such vitamin A-deficient rats, a high dose injection of retinoic acid strongly stimulated the proliferation of A spermatogonia and allowed their differentiation into B spermatogonia and then into spermatocytes, but not into spermatids (Van Pelt and de Rooij, 1991; Gaemers et al., 1998c). Repeated injections of retinoic acid were necessary for spermatogonia to reach the spermatid stage successfully (Van Pelt and de Rooij, 1991). Huang and Marshall (1983) suggested that vitamin A deficiency may delay spermatiation. Therefore, retinoids appear indispensable to the proliferation and differentiation of A spermatogonia, during their transition to round and elongated spermatids and spermatiation.

RAR-α mutant mice display germinal epithelium degeneration very similar to that of vitamin A-deficient animals (Luftkin et al., 1993). The location of RAR-α expression in the germ cells implies that retinoic acid exerts its effect on these cells via RAR-α (Akmal et al., 1997; Dufour and Kim, 1999). RXR-β mutant mice are sterile, possibly because of deficient Sertoli cell functions (Kastner et al., 1996), as a gradual accumulation of lipids was observed in Sertoli cells well before the usual degeneration of the germinal epithelium that occurs in old males. In addition, in the seminiferous tubules, RXR-β was expressed only in Sertoli cells (Kastner et al., 1996; Dufour and Kim, 1999).

Retinoids can also be harmful at excessively high doses. Hypervitaminosis A in rats reduces the testicular mass, creates lesions in the seminiferous epithelium and perturbs the rhythm of spermatogenesis (Biswas and Deb, 1965; Lamano Carvalho et al., 1978). As a result, the production of mature spermatozoa decreases and immature germ cells are extruded into the lumen of the seminiferous tubules. High doses of 13-cis retinoic acid, a very stable retinoid, block spermatogenesis completely (Sadek and Abdul-Mohsen, 1999).

**Retinoids and steroidogenesis**

In adult rats, vitamin A deficiency reduced basal testosterone secretion but testosterone secretion stimulated by exogenous LH remained similar to that of control rats (Appling and Chytil, 1981). This finding was supported by earlier reports of the atrophy of the accessory sex organs (prostate and seminal vesicles) and the female-type fine fur of vitamin A-deficient male rats (Thompson et al., 1964). Hypervitaminosis A or injection of 13-cis retinoic acid reduced the volume of testicular interstitial tissue and the mass of the seminal vesicles, and degraded the cytoplasm of Leydig cells (Biswas and Deb, 1965; Lamano Carvalho et al., 1978; Sadek and Abdul-Mohsen, 1999). These findings show that, in the same way as for spermatogenesis, both retinoid excess and retinoid deficiency are harmful to steroidogenesis.

The mechanism of action of retinoids is partly known. In adult rats, retinoids increased basal testosterone secretion in Leydig cell primary cultures but reduced this secretion when stimulated by LH (Chaudhary et al., 1989). These apparently contradictory findings were accounted for by the results of the studies conducted on cell lines that originated from Leydig cells (LeFèvre et al., 1994; Lee et al., 1999) showing that retinol and retinoic acid reduce the expression of LH receptors and greatly increase the expression of certain enzymes involved in steroidogenesis, such as P450 C17α-hydroxylase–C17-20 lyase and steroidogenic acute regulatory protein. Thus, the predominant negative effect of retinoids on LH-stimulated testosterone secretion appears to be the reduction of the expression of LH receptors.

As with other specific functions, retinoids reduce basal testosterone production in fetal Leydig cells for a short period after testis differentiation (Livera et al., 2000) and, thus, the action of retinoic acid on Leydig cells differs between the adult and the fetus (Habert et al., 2001).

**Conclusion**

Retinoids are clearly involved in the regulation of testicular functions, and much progress has been made in understanding their mechanisms of action, although this understanding is far from complete. Research to date into the effects, mode of action and physiological involvement of retinoids in testicular functions has been conducted exclusively in rodents. It is important now to determine whether the therapeutic use of retinoids affects testicular functions in men.
The authors wish to thank U. Reichert (Galderna R&D), for the gift of synthetic analogues of the different RARs and RXRs, and M. Faro, for helpful technical assistance. G. Livera is the recipient of a fellowship from the Ministère de l’Education Nationale de la Recherche et de la Technologie.

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