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MEETING REPORT

RECENT ADVANCES IN TRANSLATIONAL RESEARCH IN THE FIELD OF ENDOCRINOLOGY

HIGHLIGHTS FROM THE ANNUAL CONFERENCE OF THE SOCIETY FOR ENDOCRINOLOGY (BES), APRIL 11-14, 2011, BIRMINGHAM, U.K.

P. Bandyopadhyay

Sandwell and West Birmingham Hospitals NHS Trust, Lyndon, West Bromwich, West Midlands, UK

CONTENTS

SUMMARY

The Annual Conference of the Society for Endocrinology (BES) took place on April 11-14, 2011, in Birmingham, U.K. The meeting was devoted to new developments in different areas of endocrinology, such as thyroid disorders, endocrine tumors, obesity, reproductive endocrinology, diabetes, abnormalities of adrenal function, bones and parathyroid, growth and development, and other aspects of basic and molecular endocrinology. Translational research is a new and rapidly evolving domain that provides knowledge, understanding and perspective in diabetes, endocrinology and metabolism.

INTRODUCTION

In recent years, significant progress has been made in the understanding of the pathogenesis of many endocrine disorders. As our knowledge of the molecular control systems improves, we will be able to provide more effective treatment that offers a better end result with a higher degree of specificity and less toxicity. In developing novel drugs for the treatment of endocrine and metabolic diseases, there has been an increasing recognition of the importance of multifaceted actions. Accordingly, the design of two or more therapeutic mechanisms in a single molecular entity is becoming an exciting frontier in therapeutics. Recent advances in the understanding of the molecular mechanisms involved in the pathogenesis of these endocrine disorders greatly contribute to making the exact diagnosis and selecting the most appropriate type of treatment.

Correspondence: Prabirkumar Bandyopadhyay, MD, DM, MRCP (UK), FACP (USA), Associate Specialist in Diabetes and Endocrinology, Co-investigator in the Sandwell Medical Research Unit, Sandwell and West Birmingham Hospitals NHS Trust, Lyndon, West Bromwich, West Midlands B71 4HJ, UK. E-mail: prabirbanerjee@yahoo.co.uk.

ADVANCES IN ENDOCRINOLOGY

Adrenocortical carcinoma (ACC) is a heterogeneous neoplasm with an incompletely understood pathogenesis and an unsatisfactory prognosis. Activated signaling pathways, such as insulin-like growth factor II (IGF-II), steroidogenic factor 1 (SF-1) and β-catenin pathways, play an important role in the development of ACC and also provide diagnostic and prognostic information. [^{18}F]-FDG-PET is a very sensitive test to diagnose ACC. [^{11}C]-Metomidate or [^{123}I]-iodometomidate tracers bind selectively to cytochrome P450 11B enzymes and thereby confer high specificity to ACC imaging. Survival in ACC is highly stage-dependent and the European Network for the Study of Adrenal Tumours (ENSAT) has introduced a new staging system that provides superior prognostic information. Weiss score, resection status (R0, R1 and R2) and the KI-67 proliferation index are included in the pathology reports to establish an adequate basis for treatment decisions. After complete resection, most patients benefit from adjuvant mitotane. Adjuvant radiation therapy of the tumor bed is considered, depending on the individual risk. In advanced disease, cytotoxic drugs are added to mitotane. New targeted therapies, such as insulin-like growth factor 1 receptor (IGF-I receptor) antagonists and [^{131}I]-iodometomidate, are under investigation and will provide improved treatment options (1).

The mechanisms linking obesity to cancer risk are not completely understood. The incidence of breast cancer increases with age and the majority of these tumors are estrogen receptor (ER)-positive. Extragonadal sites, such as brain, bone and adipose tissue, synthesize estrogen from C19 steroids. The expression of aromatase, the enzyme responsible for estrogen biosynthesis, in the breast is stim-

ulated by inflammatory mediators such as PGE_2 and TNF-α produced by the tumor. 5′-AMP-activated protein kinase (AMPK) is a potent inhibitor of aromatase expression stimulated by PGE_2 in breast adipose stromal cells. Factors such as leptin and insulin are increased and adiponectin is decreased in obesity. Leptin and insulin increase the risk of breast cancer via activation of the serine/threonine-protein kinase Akt/serine/threonine-protein kinase mTOR/hypoxia-inducible factor 1-alpha (HIF-1α)/sterol regulatory element-binding protein (SREBP) pathways, and leptin and PGE_2 inhibit the serine/threonine-protein kinase LKB1/AMPK pathway, whereas adiponectin reduces the risk of breast cancer via activation of this pathway. Metformin has been shown to decrease the risk of breast cancer by stimulating AMPK and inhibiting aromatase expression. Inhibition of aromatase by metformin is breast-specific in postmenopausal women and thus leaves protected other sites of expression, such as bone and brain, where estrogens have important functions (2).

Glucagon-like peptide 1 (GLP-1) stimulates beta cell proliferation, enhances differentiation of new beta cells from progenitor cells in the pancreatic duct epithelium, inhibits apoptosis of beta cells and glucagon secretion, stimulates insulin biosynthesis and delays gastric emptying. Type 2 diabetic patients are at high risk for cardiovascular disease and these patients have impaired secretion of GLP-1. High-affinity receptors for GLP-1 are present in the heart and vascular tissue. A study from Egypt revealed significantly lower fasting GLP-1 in both type 2 diabetic patients and patients with heart failure. GLP-1 was significantly lower in diabetic patients with heart failure in comparison to nondiabetic heart failure cases. Therefore, GLP-1 deficiency might be responsible for the development of heart failure in both type 2 diabetic and nondiabetic patients (3).

Glucagon receptor agonists increase energy expenditure and GLP-1 receptor agonists prevent glucagon-induced hyperglycemia. Glucagon/GLP-1 receptor coagonists improved glucose homeostasis and reduced body weight in diet-induced obese mice. A study from London showed that both glucagon and GLP-1 have an additive effect on food intake involving same neuronal pathways activated by either hormone individually. Thus, a similar type of effect for a high dose of GLP-1 can be achieved by a combination of low doses of GLP-1 and glucagon, and this would be a novel approach to treat diabetes and obesity (4).

Thyroid hormone receptor-β (TRβ) is predominant in liver and mainly responsible for effects on cholesterol and lipoprotein metabolism, whereas thyroid hormone receptor-α (TRα) is mainly found in fat, muscle and heart. Liver-specific and TRβ-selective thyromimetics stimulate hepatic LDL receptors, cholesterol elimination as bile acids and cholesterol, and promote reverse cholesterol transport. In animal studies, these drugs reduced the progression of atherosclerosis and in humans they exerted a favorable lipid-lowering effect without having the side effects of thyroid hormone, and maintained normal hypothalamic–pituitary–thyroid feedback. Eprotirome (a TRβ analogue), when added to statins, reduced LDL and non-HDL cholesterol, apolipoprotein B, triglycerides and apolipoprotein A (5).

Low testosterone in men is associated with an increase in all-cause and cardiovascular mortality. There is a close relationship between low testosterone and metabolic syndrome. There is also a high prevalence of hypogonadism in men with type 2 diabetes. A study has shown that men with type 2 diabetes and low testosterone levels had significantly increased mortality, and testosterone replacement therapy improved survival in this group of patients (6). A retrospective audit found that testosterone undecanoate had beneficial effects on total cholesterol and LDL cholesterol in hypogonadal men but did not have any effect on HDL cholesterol, body weight and blood pressure (7).

Alterations in insulin/IGF-I signaling play an important role in life span extension in model organisms. Insulin receptor substrate 1-null mice have an increased life span and life-long insulin resistance. The mTOR pathway also appears to be important for longevity control. Global deletion of ribosomal protein S6 kinase beta-1 (S6K1), a key effector of mTOR and insulin/IGF-I signaling, extends life span in female mice. These S6K1 mice are insulin-sensitive at old age and resistant to age-related pathologies, including bone, immune and motor dysfunction. Therefore, manipulation of mTOR and AMPK may provide new options to protect against diseases of aging (8).

Breast cancer patients are at high risk of developing osteoporosis because of the low level of bioavailable estradiol induced by endocrine treatment alone or in combination with cytotoxic chemotherapy. Cancer treatment-induced bone loss is responsible for increased bone turnover and can lead to a 40-50% increase in the rate of fragility fractures. Bisphosphonate therapy is considered for patients with low bone mineral density or rapid bone loss, along with adequate calcium, vitamin D and healthy lifestyle. Studies revealed that zoledronic acid, oral bisphosphonates, as well as denosumab, an antibody to RANKL, improved bone mineral density and normalized increased bone turnover. Some data from these trials in early breast cancer also suggested that these bisphosphonates may reduce cancer recurrence rate in the adjuvant setting (9).

The long-term effect of zoledronic acid in the treatment of osteoporosis was investigated in an extension of the HORIZON Pivotal Fracture Trial. A total of 1,233 women who received zoledronic acid for 3 years in the core study were randomly allocated to an additional 3 years of zoledronic acid or blinded placebo. The primary endpoint was the percentage change in femoral neck bone mineral density at 6 years relative to 3 years. Secondary endpoints included other bone mineral density sites, bone turnover markers, fractures and safety. The combined results of bone mineral density and fractures suggest that patients at high risk for fractures, particularly vertebral fracture, should continue on annual zoledronic acid therapy (10).

Epidemiological studies suggest that hypovitaminosis D is common in patients with primary hyperparathyroidism. These patients are more vulnerable to have fractures than vitamin D-replete patients. There are concerns that vitamin D repletion in these patients might exacerbate preexisting hypercalcemia. One study concluded that weekly vitamin D supplementation with 20,000 IU for a 3-month period corrects this vitamin D deficiency in patients with mild primary hyperparathyroidism without causing any significant increase in serum calcium (11).

Hypovitaminosis D is associated with an increased prevalence of type 2 diabetes and metabolic syndrome. A study showed that the serum levels of 25-hydroxyvitamin D are negatively correlated with adiposity, insulin resistance and LDL levels, and positively correlated

with adiponectin in type 2 diabetic patients. Thus, there might be a link between 25-hydroxyvitamin D and insulin resistance and a possible beneficial effect of 25-hydroxyvitamin D on cardiovascular pathology (12). Similarly, another study demonstrated that type 2 diabetic patients and patients with cardiovascular disease had a significant reduction in serum 25-hydroxyvitamin D concentrations and thus the protective role of vitamin D_3 supplementation in the development of atherosclerosis needs to be evaluated (13).

Hyponatremia is a common biochemical abnormality in hospitalized patients and can be associated with serious central nervous system (CNS) effects. It is difficult to manage in some cases. Tolvaptan is a selective vasopressin V_2 receptor antagonist found to be quite effective in correcting the hyponatremia secondary to the syndrome of inappropriate antidiuretic hormone. Tolvaptan used for over 30 days in different clinical trials restored salt and water homeostasis rapidly following short-term use and also reduced the length of hospital stay (14, 15).

Genetic abnormalities associated with thyroid cancer are quite complex and our understanding has grown significantly over the past decade, such that this type of cancer could be treated much more efficiently. Nonoverlapping activating mutations in the gene encoding the proto-oncogene tyrosine-protein kinase receptor Ret or the high affinity nerve growth factor receptor are found in about 70% of patients with papillary thyroid cancers (PTCs). In addition, mutations in effectors of the phosphoinositide 3-kinase pathway are present at various stages of the disease, but in particular in advanced thyroid cancer. The genotype and phenotype relationship is also strong in thyroid cancer. Specific mutations are associated with particular histological variants and are also responsible for biological behavior and prognosis of cancers. The *BRAF* mutation is associated with invasive PTC and these patients are more often refractory to radioactive iodine treatment. Although fine needle aspiration of thyroid nodules can discriminate between benign and malignant thyroid cancer, immunohistochemical or genetic assays can be more accurate for cytopathological diagnosis. Most oncogenic mutations in thyroid cancer result in constitutively active kinases, which provide tractable targets for pharmacological inhibition. Although cancers accumulate further genetic damage during the course of their evolution, they remain dependent on the activity of the initiating oncoprotein for viability. AZD-6474 inhibits Ret, EGFR and vascular endothelial growth factor receptor 2 (VEGFR-2), and showed promising evidence of activity in a phase III trial in patients with medullary thyroid cancer. Sorafenib inhibits VEGFR-2, Ret and possibly RAF proto-oncogene serine/threonine-protein kinase, and in two different studies it was associated with a high percentage of patients with disease stabilization and some partial responses, particularly in PTC. All these multikinase inhibitors (sorafenib, axitinib and motesanib) inhibit VEGFR-2, the receptor for VEGF, and thus have antiangiogenic activity. These new drugs do have significant side effects and the durability of their favorable effects is not yet clear. Moreover, further studies are needed to determine the impact of these drugs on mortality. In view of these uncertainties, these drugs should be considered only for patients with rapidly progressing metastatic disease, ideally as part of a clinical trial (16).

Effective medical treatments are now available for many pituitary tumor subtypes. Long-acting dopamine agonists and somatostatin analogues have the potential to control growth and shrinkage of the tumors. Long-acting dopamine agonists have favorable responses on macroprolactinoma in 90% of cases, and these include rapid reduction of prolactin levels, tumor shrinkage within days/weeks (at least by 50%), visual improvement and recovery of normal pituitary functions. Lactotroph cells shrink by over 50%, with significant reductions in the cytoplasmic and rough endoplasmic reticulum (RER) components. In acromegaly, somatostatin analogues induce tumor shrinkage in ~75% of de novo patients, with an average volume reduction of ~50%. The reduction of somatotroph cell size is modest, but diminished proliferation and angiogenesis have been demonstrated. Somatostatin analogues are also effective in treating thyroid-stimulating hormone (TSH)-secreting adenoma, with significant tumor shrinkage. Dopamine agonists are effective in restraining tumor growth in ~70% of nonfunctioning pituitary tumors which express dopamine D_2 receptors. Dopamine and somatostatin receptor subtype analysis will guide specific medical therapies for individual tumors, not only with currently available agents, but also with multiligand somatostatin analogues such as pasireotide and chimeric molecules such as dopastatin (17).

Neuroendocrine tumors (NETs) are heterogeneous and the different subgroups of this kind of tumors depend on the site of origin, histological subtype, mitotic activity and evidence of disease progression. The benefits of chemotherapy in patients with advanced pancreatic NETs are modest and associated with significant toxicity. Pancreatic NETs are usually vascular tumors with overexpression of VEGF, a key regulator of angiogenesis, and VEGFR-2, VEGFR-3, platelet-derived growth factor receptors PDGF-R-α and -β and c-Kit. Sunitinib, an orally active multitargeted tyrosine kinase inhibitor, has been shown in a phase III trial to significantly improve the progression-free survival, objective response rate and overall survival in patients with well-differentiated, progressive pancreatic NETs. Stimulation of mTOR results in angiogenesis, cell growth and proliferation. Another phase III trial used everolimus, an inhibitor of mTOR, in patients with progressive low- or intermediate-grade advanced pancreatic NET, and it was found to prolong progression-free survival. These agents appear to be effective in patients with pancreatic NETs when other treatments do not work, and they may also be effective in nonpancreatic NETs (18).

Neuroendocrine tumors of the gastrointestinal tract are a heterogeneous group of neoplasms that secrete peptides and amines. These tumors are highly vascular and they also manifest tumor-related angiogenesis. Adenosine, a major regulator of angiogenesis, is released by enhanced degradation of ATP and also during cellular stress, damage and hypoxia. Expression of adenosine receptors, particularly A_{2A} and A_{2B} receptors, was found in neuroendocrine tumors. Activation of these receptors leads to increased proliferation and secretion of chromogranin A, and targeting this adenosine signaling pathway may be useful in the management of NETs (19). Somatostatin analogues are the most effective medical treatment to control the symptoms of NETs, such as carcinoid syndrome. Octreotide lengthened the time to tumor progression in patients with midgut carcinoid. A case report revealed the effectiveness of octreotide for controlling bleeding from angiodysplasia in a patient with metastatic NET who was unfit for any surgical intervention. Therefore, somatostatin analogues could be considered as a pallia-

tive therapy for treating lower gastrointestinal bleeding in patients in whom a surgical approach is not feasible (20).

Recombinant human IGF-I (rhIGF-I) improves insulin sensitivity and glycemic control in diabetic patients. A study that was part of a randomized, double-blind, placebo-controlled trial studying detection methods for IGF-I abuse found that the administration of rhIGF-I/IGF-binding protein 3 for 28 days improved aerobic performance and insulin sensitivity and decreased fasting triglycerides in recreational athletes, without having any significant impact on body composition. The effects on lipid and glucose homeostasis were more pronounced in women than in men (21, 22).

All kinds of lipodystrophy display the full spectrum of the metabolic syndrome, which includes insulin resistance, hypertension, dyslipidemia and glucose intolerance. Although these patients have absolute or partial reduction of fat mass, they often exhibit more extreme metabolic features than obese individuals. Partial lipodystrophy may be genetic or acquired. Genetic causes of familial partial lipodystrophy (FPLD) are mostly autosomal dominant and they include mutations in *LMNA*, *PPARG*, *AKT2*, *ZMPSTE24* and *CIDEC*. However, the majority of subjects with FPLD have no genetic etiology. Fatless limbs and prominent leg veins (phlebectasia) are the main diagnostic criteria for FPLD. But a study from Oxford defined a normal ratio of central to peripheral skin-fold measurement in healthy subjects, and this ratio was markedly increased in *LMNA* mutation-positive FPLD subjects and subjects with clinical lipodystrophy but no known genetic etiology. Leptin treatment in leptin-deficient subjects improves insulin resistance, hyperglycemia and dyslipidemia. Other therapeutic options for FPLD include thiazolidenediones and bariatric surgery (23).

Obesity is a major health problem, particularly in Western countries. It is associated with other risk factors, such as hypertension, dyslipidemia and type 2 diabetes. Currently available treatment options for obesity have limited efficacy. Bariatric surgery is the only treatment that promotes a substantial weight loss and improves glycemic control. A co-agonist for both GLP-1 and the glucagon receptor was found to be effective in causing weight loss and improving glycemic control in mice and rats. A new single-peptide co-agonist that activates both GLP-1 and GIP receptors is not degraded by dipeptidyl peptidase 4. Thus, it showed long-lasting activity in rodent models and induced a greater reduction in body weight and better glycemic control than other single agonists for the GLP-1 receptor. The rational design of peptides that can simultaneously modulate the activity of several receptors involved in the control of energy metabolism may offer new pharmacological alternatives for the treatment of obesity and diabetes (24).

Bariatric surgery is associated with substantial and sustained weight loss and is the only evidence-based treatment for morbid obesity that leads to normalization of metabolic risk factors and reduction of overall mortality and the incidence of cancer. The mechanism of action of gastric bypass surgery is complex. It causes supraphysiological release of gut hormones, which include GLP-1, peptide PYY and other gut hormones promoting satiety after a test meal but no increase in the fasting state. These effects, along with changes in GIP, glucagon, etc., might contribute to weight-independent improvement in type 2 diabetes after gastric bypass surgery (25). Most evidence for the benefit of gastric bypass surgery derives from subjects who had morbid obesity. But recently, gastric bypass surgery was also studied in patients with lower body mass index. Irrespective of initial body weight, Roux-en-Y gastric bypass surgery improved insulin resistance, which was evidenced within days of surgery. There was also an improvement in insulin secretion, including restoration of first-phase loss (26). Another study found that Roux-en-Y bypass surgery reduced inflammatory markers such as CRP, reduced both systolic and diastolic blood pressure and improved endothelial function 12 months after surgery in morbidly obese patients (body mass index [BMI] > 40 kg/m^2) without type 2 diabetes (27).

It has been found that 5α-dihydrocorticosterone and 5α-tetrahydrocorticosterone, metabolites of corticosterone, possess similar antiinflammatory properties but less metabolic effects compared to corticosterone. Although the mechanism of action of these metabolites is different, both suppress inflammatory kinase pathways. Thus, these 5α-reduced glucocorticoid metabolites have the potential to be considered as "dissociated" antiinflammatory steroid therapy (28).

Genetic factors play an important role in the pathogenesis of essential hypertension. The *CYP11B2* gene encodes the aldosterone synthase enzyme. Variation of this gene is associated with excess aldosterone production, leading to hypertension. miRNAs are a class of post-transcriptional regulatory molecules implicated in cardiovascular disease, development and tumorigenesis. These classes of molecules target the 3′-untranslated region of mRNAs and inhibit translation through mRNA cleavage or destabilization. A study indentified two miRNAs, miR-125a-5p and miR-134, with aberrant expression of aldosterone producing adenoma samples and putative binding sites in the *CYP11B2* gene. miR-125a-5p and miR-125b can also repress *CYP11B2* by directly targeting the 3′-untranslated region. The regulation of *CYP11B2* mRNA by miRNAs and altered expression in adrenal adenomas may give rise to novel therapeutic targets for the treatment of essential hypertension and adrenal tumors (29).

Ten percent of hypertensive patients have primary hyperaldosteronism and one-third of them have Conn's syndrome. Adrenalectomy has the potential to cure or improve the control of hypertension. A study assessed the benefits/costs of laparoscopic adrenalectomy in a cohort of 24 consecutive patients with Conn's syndrome in a tertiary referral center. The cost averaged £3,050/patient, which is within the national tariff for adrenalectomy. Follow-up questionnaires revealed that 93% of patients reported taking no/fewer medications and 86% of patients reported improved quality of life postoperatively, and all patients stated that they would definitely have the operation again in preference to antihypertensive medications (30).

Cortisol regeneration is inhibited by 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) and this can be a promising therapeutic option to treat type 2 diabetes. In obesity, 11β-HSD1 activity is increased in adipose tissue but decreased in the liver because of hyperinsulinemia. Metformin increased whole-body 11β-HSD1 activity in euglycemic obese men. Thus, 11β-HSD1 inhibitors could be less effective in the presence of metformin, given their shared mechanism of suppressing hepatic gluconeogenesis (31).

Treatment options for Graves' disease have largely remained unchanged for the last 50 years. The relapse rate following anti-thy-

roid drug therapy is high and there are short- and long-term risks for destructive definitive therapies. Second-generation assays for thyrotropin receptor (TSH-R) antibodies offer the possibility of targeted timing of the duration of anti-thyroid drug therapy. Serum selenium levels and common genetic variations may modify the response to treatment. Prior thionamide therapy and the use of steroids also modulate the response to radioiodine treatment. The duration of exposure to high thyroid hormone levels may have an impact on cardiovascular and osteoporotic outcomes. Recently B-cell therapy was found to improve the remission rate in Graves' disease and Graves' ophthalmopathy after anti-thyroid drug therapy. Small-molecule inhibitors of TSH-R and blocking anti-TSH-R monoclonal antibodies are the new developments for more rapid induction of remission and improved outcomes in refractory cases (32).

There is partial or total deficiency of insulin in diabetes, which is responsible for hyperglycemia and a decrease in the activity of glycogenic enzymes, resulting in depletion of liver and muscle glycogen. An animal study found that *Syzygium aromaticum* derived from oleanolic acid restored the activity of the key glycogenic enzymes glucokinase and hexokinase in the liver and skeletal muscle of streptozotocin-induced diabetic rats, and thus enhanced glycogen synthesis to improve the glycemic status. Therefore, the use of oleanolic acid to treat diabetes may be a novel therapeutic strategy (33).

Blood-borne bacteria, fungi and viral agents interact with Toll-like receptors on the surface of immune cells and can activate the innate immune system. Research from Germany demonstrated that mRNA for Toll-like receptors is ubiquitously expressed in a range of transformed and normal cell types. These findings raise the possibility that infection could induce an inflammatory response in somatic tissues. This might provide an environment for changes in normal cells that lead to neoplastic growth and/or enhancing the growth of an existing neoplastic lesion. A full Toll-like receptor-mediated inflammatory system was found in breast tumor cells and these Toll-like receptors could be targeted as a new approach for tumor therapy (34).

Kisspeptin is a novel hypothalamic hormone that has powerful stimulatory effects on the hypothalamo–pituitary–gonadal axis. Pubertal failure can result from inactivating mutations in the kisspeptin receptor. Recent studies demonstrated that endogenous kisspeptin may be involved in stimulating the gonadotropin-releasing hormone (GnRH) pulse generator. Injection of kisspeptin-54 stimulates luteinizing hormone (LH) release in healthy men and women. Administration of a single injection of kisspeptin-54 in 6 healthy female volunteers increased LH pulse frequency and LH pulse amplitude. Future development of kisspeptin may lead to important therapeutic implications to treat patients with disorders of reproduction (35).

Loss of sex steroids is thought to be partially responsible for age-related cognitive decline in postmenopausal women. Similarly, the circulating estradiol level declines when old female rhesus monkeys (*Macaca mulatta*) reach menopause. They also show an age-related decline in the release of dehydroepiandrosterone (DHEA) from their adrenal glands. DHEA acts as a substrate for estradiol synthesis in the brain and it is plausible that DHEA supplementation could enhance cognitive function in the elderly. In one study, 5 mg of oral DHEA was given each morning to old ovary-intact female rhesus monkeys for 2 months, and this treatment demonstrated a detectable improvement in cognitive function. DHEA therapy is effective when it is initiated before the subjects show significant age-related attenuation of estradiol levels. The underlying mechanism is not clear, but detection of 17β-hydroxysteroid dehydrogenase, 3β-hydroxysteroid dehydrogenase and aromatase enzyme gene expression in the prefrontal cortex and hippocampus suggests that it may involve intracrine conversion of DHEA to estradiol within the CNS (36).

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DISCLOSURES

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