Ankara Üniv Vet Fak Derg, **60**, 79-83, 2013

Derleme / *Review*

A new strategy in treatment of neurodegenerative diseases: Neurosteroids

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Summary: Steroid synthesized from cholesterol in the central nervous system independently of gonads and adrenal glands has been defined as neurosteroids. Neurosteroids are synthesized in many species of vertebrate and invertebrate nervous systems. Neurosteroids affects the many brain functions. The expression of enzymes catalyzing the synthesis of neurosteroids and the neurosteroid levels are changes in diseases of the nervous system. It has been well documented that neurosteroids protective role on the neurons. Neurosteroids reduces the disorders associated with nervous system in neurodegenerative diseases and can be used as preventive and therapeutic in these diseases.

Key words: Neurodegenerative diseases, neurosteroid.

Nörodejeneratif hastalıkların tedavisinde yeni bir strateji: Nörosteroidler

Özet: Merkezi sinir sisteminde gonadlardan ve adrenal bezlerden bağımsız olarak kolesterolden sentezlenen steroid nörosteroid olarak tanımlanır. Pek çok omurgalı ve omurgasız canlıların sinir sisteminde nörosteroidler sentezlenmektedir. Nörosteroidler pek çok beyin fonksiyonunu etkilemektedir. Sinir sistemi hastalıklarında nörosteroid sentezini katalizleyen enzimlerin ekspresyonları ve nörosteroid düzeyleri değişmektedir. Nörosteroidlerin nöronlar üzerinde koruyucu etkiye sahip olduğu iyi bilinmektedir. Nörosteroidler nörodejeneratif hastalıklarda sinir sistemine ilişkin bozuklukları hafifletmekte, koruyucu ve tedavi edici olarak kullanılabilmektedir.

Anahtar sözcükler: Nörodejeneratif hastalıklar, nörosteroid.

Steroid synthesized from cholesterole in central nervous system independently of gonads and adrenal glands is called neurosteroid. The synthesis of neurosteroids in central nervous system have been well documented (14, 46, 47, 67). Neurosteroids have been widely recognized to modulate brain cell properties and functions (3, 10, 17, 36). Pregnenolone and pregnenolone sulphate play an essential role in the process of memory and learning (3, 17, 34, 39). The 3-alpha-hydroxy metabolites of progesterone have anaesthetic effects (45). New findings have been obtained that the progesterone prevents depression-like behavior (10). Neurosteroids have been shown to protective effects on neurons and glial cells and therapeutic effects of the neurosteroids have been investigated in neurodegeneration (8, 9, 18, 49). The antidepressant and neuroprotective effects of dehydroepiandrosterone have been reported (9, 32, 58). Testosterone has also been proposed as neuroprotective agents (2, 51). Through experimental and clinical studies, neuroprotective effects of estradiol have been recognized (8, 22, 24, 57). In this review, neurosteroid biyosynthesis in central nervous system, changes of neurosteroids in neurodegenerative diseases and therapeutic possibilities of neurosteroids was summarized.

Biosynthesis of neurosteroids in central nervous system

Neurosteroids are syntehsized from cholesterole *de novo* by neurons and glial cells. The expressions of steroidogenic enzymes including P450scc (50, 53), 3β-hydroxysteroid dehydrogenase/Δ^5-Δ^4-isomerase (3β-HSD) (51), P450 17α-liyase (11), 17-β-hydroxysteroid dehydrogenase (17β-HSD) (37) and P450 aromatase (26, 28, 42, 66) in the central nervous system were demonstrated in mammalian and non-mammalian vertebrates. P450scc transforms cholesterol into pregnenolone which is a precusor of dehydroepiandrosterone. Progesterone is formed from pregnenolone by the 3β-HSD. Both progesterone and DHEA are converted into testosterone. Testosterone is converted into estradiol by P450 aromatase. The expression of 3β-HSD has been well demonstrated in the oligodendrocytes and Purkinje neurons in cerebellar cortex of dogs (64). In ependymal cells of the choroid plexus in sheep, an apparent

cytoplasmic immunoreactivity of the 3β-HSD which catalyzes the dehydrogenation of the pregnenolone into progesterone has been found. An immunoreactivity of the 3β-HSD suggests progesterone most likely be synthesized locally in the sheep choroid plexus (29). It has been also measured the concentrations of progesterone in the specific central nervous system regions such as cortex (frontal, parietal, temporal, occipital), corpus callosum, cerebellum and medulla oblongata of the ram and anestrous ewe (61). Progesterone concentrations have been recorded as high in the frontal cortex, and low in the medulla oblongata both ram and ewe. No significant differences have been determined between the ram and ewe for any central nervous system regions.

The changes of neurosteroids in neurodegenerative diseases

Changes in and neurosteroid levels and their steroidogenic enzyme expressions are involved in physiopathological conditions. Aromatase expression is up-regulated during the brain injury in mamalian and birds (22, 43). The concentration of cerebrospinal fluid pregnenolone are decreased in patients with affective depression (23). It has been indicated that decreased progesterone concentration in the cerebellum in canine distemper virus infection suggesting that local impairment of progesterone synthesis may be associated with the initiation and progression of cerebellar lesions (62). With previous findings as a background, to understand the mechanisms of demyelination and remyelination in neurodegeneration, has been recently examined myelin basic protein profiles in experimentally demyelinated and remyelinated mice (60). In the demyelinated mice, myelin basic protein band intensity was significantly thinner than the healthy mice and in the remylinated mice it increased in a significant manner and approached to values of control group. Recently, it has been investigated age-dependent changes of neurosteroids including estradiol, progesterone, testosterone and dehydroepiandrosterone in cerebellum and frontal cortex, parietal cortex and temporal cortex of newborn 1, 6, 12, 24-month-old male Sprague-Dawley rats. Progesterone concentration of central nervous system regions increased slightly during aging period and was inversely related to age of rats. No significant differences have been found between newborn, 1, 6, 12, 24-month-old rats for estradiol, testosterone and dehydroepiandrosterone (16). Higher expression of the 3β-HSD in astrocytes of the demyelinated site in canine distemper virus infection has been postulated (64). An overexpression of aromatase has been demonstrated in the cerebellum of dogs infected with canine distemper virus (63). Furthermore, overexpression of the aromatase in astrocytes in areas of demyelination has been determined using Western-blot analysis in cuprisone induced demyelination in C57Bl/6 mice (65).

Preventive and therapeutic use of neurosteroids in neurodegenerative diseases

A large number of studies support the neurosteriods have neuroprotective, myelinating, antiapoptotic and antienflamatuar effects (4, 11, 25, 35, 44, 55). Combined administration of 17β-estradiol and progesterone have been demonstrated protect the brain from demyelination and stimulate remyelination (1). Progesterone are considered to play a major role in myelin formation (7, 27). Estriol and progesterone have been demonstrated inhibit microglial production of nitric oxide which be toxic to oligodendrocytes, in a dose-dependent manner (20). Progesterone exerts neuroprotective effects in traumatic central nervous system injury and motoneuron degeneration (18). A study by Garay et al. (21) suggested that administration of progesterone enhances the myelination in the experimental autoimmune encephalomyelitis model of multiple sclerosis. It has also been found that progesterone prevents depression-like behavior in a model of Parkinson's disease rats (10). Progesterone and allopregnanolone administrations reduce the cell death, gliosis, and functional deficits after traumatic brain injury (19). Allopregnanolone also exerts an analgesic effect in the experimental pain model (30, 38, 56).

Through experimental and clinical studies, neuroprotective effects of estradiol have been recognized (8, 22, 24, 57). It has been found that estradiol promotes myelin formation after its neonatal administration (15). Beneficial effects of progesterone in treatment of functional recovery of traumatic brain injury have been reported (54). Recently has been demonstrated that estradiol treatment is a potentially useful to enhance recovery after ischemic injury (41). An experimental study has shown the estriol treatment reduce the severity of autoimmune encephalomyelitis (31). It has been postulated that hormonal alterations during gestation have a protective effect on the course of multiple sclerosis (59). Additionally, estriol treatment with the pregnancy doses has been found to be effective in treatement of nonpregnant female multiple sclerosis patients (48). Administration of 17-beta-estradiol protect oligodendrocytes from cytotoxicity in a dose-dependent manner (49). Neuroprotective effects of estrogen have also been demonstrated in experimental models of Parkinson's disease (5, 13, 40).

Dehydroepiandrosterone has been reported to protect hippocampal neurons against neurotoxication (9, 32). DHEA has been shown to inhibit production of proinflammatory cytokines tumor necrosis factor alpha and interleukin-6 in astrocytes (30). Importantly, dehydroepiandrosterone inhibits interferon-gamma production by microglia that is critical for innate and adaptive immunity (6).

In recent years, testosterone has been proposed as neuroprotective agents in treatments of neurodegenerative diseases. Testosterone protects cerebellar granule cells from cell death induced by oxidative stress (2). It has been reported that treatment with testosterone by intracerebral ventricular injection regenerates the spinal motoneurons in sciatic nerve crush model in rat (51).

Conclusion

The synthesis of neurosteroids in the central nervous system in mammalian and non-mammalian vertebrates have been well documented. Neurosteroids mediates brain cell properties and functions. The expression of enzymes catalyzing the synthesis of neurosteroids and the neurosteroid levels are changes in diseases of the nervous system. Through experimental studies and clinical trials, neuroprotective effects of neurosteroids have been recognized. Neurosteroids have many effects including myelinating, antiapoptotic, antienflamatuar and antidepressant. Recently, neuroactive steroids used as preventive and therapeutical in various neurodegenerative diseases such as multiple sclerosis, Parkinson's disease, autoimmune encephalomyelitis, traumatic brain injury and ischemic injury.

References

1. **Acs P, Kipp M, Norkute A, Johann S, Clarner T, Braun A, Berente Z, Komoly S, Beyer C** (2009): *17β-estradiol and progesterone prevent cuprizone provoked demyelination of corpus callosum in male mice*. Glia, **57,** 807-814.
2. **Ahlbom E, Prins GS, Ceccatelli S** (2001): *Testosterone protects cerebellar granule cells from oxidative stress-induced cell death through a receptor mediated mechanism*. Brain Res, **892**, 255-262.
3. **Akwa Y, Ladurelle N, Covey DF, Baulieu EE** (2001): *The synthetic enantiomer of pregnenolone sulfate is very active on memory in rats and mice, even more so than its physiological neurosteroid counterpart: distinct mechanisms?* Proc Natl Acad Sci USA **98**, 14033-14037.
4. **Azcoitia I, Leonelli E, Magnaghi V, Veiga S, Garcia-Segura LM, Melcangi RC** (2003): *Progesterone and its derivatives dihydroprogesterone and tetrahydroprogesterone reduce myelin fiber morphological abnormalities and myelin fiber loss in the sciatic nerve of aged rats*. Neurobiol Aging, **24,** 853-860.
5. **Baraka AM, Korish AA, Soliman GA, Kamal H** (2011): *The possible role of estrogen and selective estrogen receptor modulators in a rat model of Parkinson's disease*. Life Sci, **88,** 879-885.
6. **Barger SW, Chavis JA, Drew PD** (2000): *Dehydroepiandrosterone inhibits microglial nitric oxide production in a stimulus-specific manner*. J Neurosci Res, **62**, 503-509.
7. **Baulieu E, Schumacher M** (2000): *Progesterone as a neuroactive neurosteroid, with special reference to the effect of progesterone on myelination*. Steroids, **65**, 605-612.
8. **Behl C, Widmann M, Trapp T, Holsboer F** (1995): *17-Estradiol protects neurons from oxidative stress-induced cell death in vitro*. Biochem Biophys Res Commun, **216**, 473-482.
9. **Cardounel A, Regelson W, Kalimi M** (1999): *Dehydroepiandrosterone protects hippocampal neurons against neurotoxin-induced cell death: mechanism of action*. Proc Soc Exp Biol Med, **222**, 145-149.
10. **Casas S, García S, Cabrera R, Nanfaro F, Escudero C, Yunes R** (2011): *Progesterone prevents depression-like behavior in a model of Parkinson's disease induced by 6-hydroxydopamine in male rats*. Pharmacol Biochem Behav, **4,** 614-618.
11. **Charalampopoulos I, Tsatsanis C, Dermitzaki E, Alexaki VI, Castanas E, Margioris AN, Gravanis A** (2004): *Dehydroepiandrosterone and allopregnanolone protect sympathoadrenal medulla cells against apoptosis via antiapoptotic Bcl-2 proteins*. Proc Natl Acad Sci USA, **101,** 8209–8214.
12. **Compagnone NA, Bulfone A, Rubenstein JL, Mellon SH** (1995): *Steroidogenic enzyme P450c17 is expressed in the embryonic central nervous system.* Endocrinology, **136,** 5212–5223
13. **Cordellini MF, Piazzetta G, Pinto KC, Delattre AM, Matheussi F, Carolino RO, Szawka RE, Anselmo-Franci JA, Ferraz AC** (2011): *Effect of different doses of estrogen on the nigrostriatal dopaminergic system in two 6-hydroxydopamine-induced lesion models of Parkinson's disease.* Neurochem Res, **36,** 955-961.
14. **Corpéchot C, Synguelakis M, Talha S, Axelson M, Sjövall J, Vihko R, Baulieu EE, Robel P** (1983): *Pregnenolone and is sulfate ester in rat brain*. Brain Res, **270**, 119-125.
15. **Curry JJ 3rd, Heim LM** (1966): *Brain myelination after neonatal administration of oestradiol*. Nature, **209**, 915-916.
16. **Çiftci G, Yarım GF, Yarım M, Karayiğit MO, Çenesiz S, Nisbet C, Gültiken ME** (2011): *The effects of aging on central nervous system steroid prophiles and myelin basic protein in rats*. Aging Clin Exp Res, (In Press).
17. **Darnaudéry M, Pallarès M, Piazza PV, Le Moal M, MayoW** (2002): *The neurosteroid pregnenolone sulfate infused into the medial septum nucleus increases hippocampal acetylcholine and spatial memory in rats*. Brain Res, **951**, 237-242.
18. **De Nicola AF, Labombarda F, González Deniselle MC, González SL, Garay L, Meyer M, Gargiulo G, Guennoun R, Schumacher M** (2009): *Progesterone neuroprotection in traumatic CNS injury and motoneuron degeneration*. Front Neuroendocrinol, **30,** 173-187.
19. **Djebaili M, Guo Q, Pettus EH, Hoffman SW, Stein DG** (2005): *The neurosteroids progesterone and allopregnanolone reduce cell death, gliosis, and functional deficits after traumatic brain injury in rats.* J Neurotrauma, **22,** 106-118.
20. **Drew PD, Chavis JA** (2000): *Sex steroid regulation of microglial cell activation: relevance to multiple sclerosis*. J Neuroimmunol, **111**, 77-85.
21. **Garay L, Gonzalez Deniselle MC, Gierman L, Meyer M, Lima A, Roig P, De Nicola AF** (2008): *Steroid protection in the experimental autoimmune encephalomyelitis*

model of multiple sclerosis. Neuroimmunomodulation, **15,** 76-83.

22. **Garcia-Segura LM, Wozniak A, Azcoitia I, Rodriguez JR, Hutchison RE, Hutchison JB** (1999): *Aromatase expression by astrocytes after brain injury: implications for local estrogen formation in brain repair*. Neuroscience, **89**, 567-578.
23. **George MS, Guidotti A, Rubinow D, Pan B, Mikalauskas K, Post RM** (1994): *CSF neuroactive steroids in affective disorders: pregnenolone, progesterone and DBI*. Biol Psychiatry, **35,** 775-780.
24. **Green PS, Simpkins JW** (2000): *Neuroprotective effects of estrogens: potential mechanisms of action*. Int J Dev Neurosci, **18**, 347-358.
25. **He J, Evans CO, Hoffman SW, Oyesiku NM, Stein DG** (2004): *Progesterone and allopregnanolone reduce inflammatory cytokines after traumatic brain injury*. Exp Neurol, **189,** 404-412.
26. **Hojo Y, Hattori TA, Enami T, Furukawa A, Suzuki K, Ishii HT, Mukai H, Morrison JH, Janssen WG, Kominami S, Harada N, Kimoto T, Kawato S** (2004): *Adult male rat hippocampus synthesizes estradiol from pregnenolone by cytochromes P45017alpha and P450 aromatase localized in neurons*. Proc Natl Acad Sci USA. **101,** 865-870.
27. **Ibanez C, Shields SA, El-Etr M, Baulieu EE, Schumacher M, Franklin RJ** (2004): *Systemic progesterone administration results in a partial reversal of the age-associated decline in CNS remyelination following toxin-induced demyelination in male rats.* Neuropathol Appl Neurobiol, **30**, 80-89.
28. **Ivanova T, Beyer C** (2000): *Ontogenetic expression and sex differences of aromatase and estrogen receptor-alpha/beta mRNA in the mouse hippocampus*. Cell Tissue Res, **300,** 231–237
29. **Karahan S, Yarım GF, Yarım M** (2007): *Choroid epithelial cells: source cerebrospinal fluid progesterone in sheep?*. Med Weter, **63,** 935-937
30. **Kavaliers M, Wiebe JP** (1987): *Analgesic effects of the progesterone metabolite, 3 alpha-hydroxy-5 alpha-pregnan-20-one, and possible modes of action in mice.* Brain Res, **415,** 393-398.
31. **Kim S, Liva SM, Dalal MA, Verity MA, Voskuhl RR** (1999): *Estriol ameliorates autoimmune demyelinating disease: implications for multiple sclerosis*. Neurology, **52,** 1230-1238.
32. **Kimonides VG, Khatibi NH, Svendsen CN, Sofroniew MV, Herbert J** (1998): *Dehydroepiandrosterone (DHEA) and DHEA-sulfate (DHEAS) protect hippocampal neurons against excitatory amino acid-induced neurotoxicity*. Proc Natl Acad Sci USA, **95,** 1852-1857.
33. **Kipper-Galperin M, Galilly R, Danenberg HD, Brenner T** (1999): *Dehydroepiandrosterone selectively inhibits production of tumor necrosis factor alpha and interleukin-6 [correction of interlukin-6] in astrocytes.* Int J Dev Neurosci, **17**, 765-775.
34. **Ladurelle N, Eychenne B, Denton D, Blair-West J, Schumacher M, Robel P, Baulieu E** (2000): *Prolonged intracerebroventricular infusion of neurosteroids affects cognitive performances in the mouse*. Brain Res, **858**, 371-379.
35. **Mayo W, Lemaire V, Malaterre J, Rodriguez JJ, Cayre M, Stewart MG, Kharouby M, Rougon G, Le Moal M, Piazza PV, Abrous DN** (2005): *Pregnenolone sulfate enhances neurogenesis and PSA-NCAM in young and aged hippocampus*. Neurobiol Aging, **26,** 103-114.
36. **Mc Ewen BS, Biegon A, Davis PG, Krey LC, Luine VN, McGinnis MY, Paden CM, Parsons B, Rainbow TC** (1982): *Steroid hormones: humoral signals which alter brain cell properties and functions.* Recent Prog Horm Res, 38, 41-92.
37. **Mellon SH, Deschepper CF** (1993): *Neurosteroid biosynthesis: genes for adrenal steroidogenic enzymes are expressed in the brain*. Brain Res, **629,** 283-292.
38. **Meyer L, Patte-Mensah C, Taleb O, Mensah-Nyagan AG** (2011): *Allopregnanolone prevents and suppresses oxaliplatin-evoked painful neuropathy: multi-parametric assessment and direct evidence*. Pain, **152,** 170-181.
39. **Meziane H, Mathis C, Paul SM, Ungerer A** (1996): *The neurosteroid pregnenolone sulfate reduces learning deficits induced by scopolamine and has promnestic effects in mice performing an appetitive learning task*. Psychopharmacology, **126**, 323-330.
40. **Morissette M, Al Sweidi S, Callier S, Di Paolo T** (2008): *Estrogen and SERM neuroprotection in animal models of Parkinson's disease*. Mol Cell Endocrinol, **290,** 60-69.
41. **Perez-Alvarez MJ, Maza MD, Anton M, Ordoñez L, Wandosell F** (2012): *Post-ischemic estradiol treatment reduced glial response and triggers distinct cortical and hippocampal signaling in a rat model of cerebral ischemia.* J Neuroinflamm, **9,** 157.
42. **Peruffo A, Giacomello M, Montelli S, Corain L, Cozzi B** (2011): *Expression and localization of aromatase P450AROM, estrogen receptor-α, and estrogen receptor-β in the developing fetal bovine frontal cortex.* Gen Comp Endocrinol, **172,** 211-217.
43. **Peterson RS, Saldanha CJ, Schlinger BA** (2001): *Rapid upregulation of aromatase mRNA and protein following neural injury in the zebra finch (Taeniopygia guttata)*. J Neuroendocrinol, **4**, 317-323.
44. **Pettus EH, Wright DW, Stein DG, Hoffman SW** (2005): *Progesterone treatment inhibits the inflammatory agents that accompany traumatic brain injury*. Brain Res, **1049,** 112-119.
45. **Phillipps GH** (1975): *Structure-activity relationships in steroidal anaesthetics*. J Steroid Biochem, **6**, 607-613.
46. **Robel P, Baulieu EE** (1985): *Neuro-steroids, 3β-hydroxy-Δ-5-derivatives in the rodent brain*. Neurochem Int, **7**, 953-958.
47. **Robel P, Bourreau E, Corpechot C, Dang DC, Halberg F, Clarke C, Haug M, Schlegel ML, Synguelakis M, Vourch C** (1987): *Neuro-steroids: 3 beta-hydroxy-delta 5-derivatives in rat and monkey brain*. J Steroid Biochem, **27**, 649-655.
48. **Sicotte NL, Liva SM, Klutch R, Pfeiffer P, Bouvier S, Odesa S, Wu TC, Voskuhl RR** (2002): *Treatment of multiple sclerosis with the pregnancy hormone estriol.* Ann Neurol, **52,** 421-428.
49. **Takao T, Flint N, Lee L, Ying X, Merrill J, Chandross KJ** (2004): *17beta-estradiol protects oligodendrocytes from cytotoxicity induced cell death*. J Neurochem, **89**, 660-673.

50. **Takase M, Ukena K, Yamazaki T, Kominami S, Tsutsui K** (1999): *Pregnenolone, pregnenolone sulfate, and cytochrome P450 side-chain cleavage enzyme in the amphibian brain and their seasonal changes*. Endocrinology, **140**, 1936-1944.
51. **Tehranipour M, Moghimi A** (2010): *Neuroprotective effects of testosterone on regenerating spinal cord motoneurons in rats.* J Mot Behav, **42**, 151-155.
52. **Ukena K, Kohchi C, Tsutsui K (**1999): *Expression and activity of 3β-hydroxysteroid dehydrogenase/Δ5-Δ4-isomerase in the rat Purkinje neuron during neonatal life.* Endocrinology, **140,** 805-813.
53. **Ukena K, Usui M, Kohchi C, Tsutsui K** (1998): *Cytochrome P450 side-chain cleavage enzyme in the cerebellar Purkinje neuron and its neonatal change in rats*. Endocrinology, **139**, 137-147.
54. **Vandromme M, Melton SM, Kerby JD** (2008): *Progesterone in traumatic brain injury: time to move on to phase III trials*. Crit Care, **12**, 153.
55. **Wang JM, Singh C, Liu L, Irwin RW, Chen S, Chung EJ, Thompson RF, Brinton RD** (2010): *Allopregnanolone reverses neurogenic and cognitive deficits in mouse model of Alzheimer's disease*. Proc Natl Acad Sci USA, **107,** 6498-6503.
56. **Winfree CJ, Coombs DW, DeLeo JA, Colburn RW** (1992): *Analgesic effects of intrathecally-administered 3 alpha-hydroxy-5 alpha-pregnan-20-one in a rat mechanical visceral pain model.* Life Sci, **50,** 1007-1012.
57. **Wise PM, Dubal DB, Wilson ME, Rau SW** (2000): *Estradiol is a neuroprotective factor in in vivo and in vitro models of brain injury*. J Neurocytol, **29**, 401-410.
58. **Wolkowitz OM, Reus VI, Roberts E, Manfredi F, Chan T, Raum WJ, Ormiston S, Johnson R, Canick J, Brizendine L, Weingartner H** (1997): *Dehydroepiandrosterone (DHEA) treatment of depression*. Biol Psychiatry, **41**, 311-318.
59. **Worthington J, Jones R, Crawford M, Forti A** (1994): Pregnancy and multiple sclerosi--a 3-year prospective study. J Neurol, **241,** 228-233.
60. **Yarım GF, Ciftci G, Yarım M, Karayiğit MO** (2011): *Myelin basic protein profile in experimentally demyelinated and remyelinated mice.* Third East Mediterranean International Council for Laboratory Animal Science Symposium, İstanbul, Türkiye, p. 93.
61. **Yarım GF, Karahan S** (2007): *Regional brain and sex differences in the plasma progesterone concentration of sheep*. Small Rum Res, **71,** 98-102.
62. **Yarım GF, Karahan S, Yarım M** (2007): *Cerebellum progesterone concentration decreased in canine distemper virus infection*. Res Vet Sci, **82**, 173-180.
63. **Yarım M, Gülbahar MY, Güvenç T, Karahan S, Harada N, Kabak YB, Karayiğit MO** (2010): *Aromatase Expression in the Cerebellum of the dog infected with canine distemper virus*. Berl Munch Tierarztl, **123,** 301-306.
64. **Yarım M, Kabakcı N** (2002): *Distribution of 3beta-hydroxysteroid dehydrogenase in the cerebellum in canine distemper virus infection*. J Comp Path, **127,** 290-296.
65. **Yarım M, Karayiğit MO, Çiftci G** (2011): *Association of aromatase and 3β-HSD with cuprizone induced demyelination and remyelination in C57Bl/6 mice*. 29th Meeting of The European Society of Veterinary Pathology and The European College of Veterinary Pathologists, 9th European Congress of Toxicologic Pathology of The European Society of Toxicologic Pathology, Uppsala, Sweden, p. 75.
66. **Zwain IH, Yen SS, Cheng CY** (1997): *Astrocytes cultured in vitro produce estradiol-17beta and express aromatase cytochrome P-450 (P-450 AROM) mRNA*. Biochim Biophys Acta, **1334**, 338-348.
67. **Zwain IH, Yen, SSC** (1999): *Neurosteroidogenesis in astrocytes, oligodendrocytes and neurons of cerebral cortex of rat brain.* Endocrinology, **140**, 3843-3852.

Geliş tarihi: 22.02.2012 / Kabul tarihi: 17.07.2012

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