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Zoological Research

Effects of Oestrogen on Ischemia-induced Neurogenesis in the Dentate Gyrus of Rats

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Abstract: To study the effects of oestrogen on ischemia-induced neurogenesis in the hippocampal dentate gyrus, thirty-two adult male rats were randomly divided into four groups: the control surgery group with oestrogen administration (SE), the control surgery group with normal saline administration (SN), the middle cerebral artery occlusion (MCAO) group with oestrogen administration (ME) and the MCAO group with normal saline administration (MN). The MCAO rats were occluded for 90 min by an intraluminal filament and then recirculated. After 1, 3, 12, 24 and 28 h of MCAO, the rats of the four groups were killed to investigate the infarct volume, apoptosis and neurogenesis. The cerebral infarct volume in the ME group was significantly smaller than that of the MN group ($P < 0.05$). No significant cell loss was seen in the dentate gyrus. Cerebral ischemia led to increased neurogenesis, which is independent of cell death in the ipsilateral dentate gyrus ($P < 0.05$). BrdU-positive cells in the ipsilateral dentate gyrus of the ME group were significantly increased when compared with those of the MN group ($P < 0.05$). In the SE group, BrdU-positive cells in both the ipsilateral and contralateral dentate gyrus, were increased when compared with those of the SN group ($P < 0.05$). We concluded that oestrogen plays an important role in neurogenesis, which is independent of ischemia-induced by MCAO in the hippocampal dentate gyrus of rats.

Key words: Cerebral ischemia; Infarct volume; Neurogenesis; Oestrogen; Cell death; Dentate gyrus

雌激素在脑缺血诱导的大鼠齿状回神经再生中的作用

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摘要: 为研究雌激素对成年动物局灶性脑缺血诱导成年动物海马齿状回神经元再生的影响, 将雄性 SD 大鼠分为假手术 + 雌激素组(SE)、假手术 + 生理盐水替代组(SN)、缺血 + 雌激素组(ME)和缺血 + 生理盐水替代组(MN), 右侧大脑中动脉闭塞(MCAO)建立脑缺血模型。在缺血 90 min 后恢复供血再灌注, 分别于再灌注后 1、3、12、24 和 28 h 处死老鼠并检测各组大鼠脑梗死体积、细胞凋亡以及脑缺血诱导的成年动物海马齿状回神经元再生的情况。在 5 个时间点的检测中, ME 组脑梗死体积显著小于 SE 组($P < 0.05$); 在 MCAO 大鼠中, 海马齿状回区域并未发现有神经元丢失及凋亡的现象。同时, MN 组与 SN 组相比较, 损伤侧齿状回新生神经元数目明显增多($P < 0.05$), 说明这种缺血诱导的神经元再生并不依赖于齿状回区域神经细胞的死亡; ME 组与 MN 组相比较, 损伤侧新生神经元数目显著增多($P < 0.05$); SE 与 SN 组相比较, 手术侧和对侧的新生神经元数目都显著增加($P < 0.05$)。结果提示雌激素对局灶性脑缺血后海马齿状回神经元再生具有促进作用, 且这种促进作用与海马缺血损伤程度无关。

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There is a ccumulating evidence that neurogenesis continues throughout adulthood in the dentate gyrus in many species of animals (Kaplan & Hinds, 1977; Gould & Tanapat 1997; Eriksson et al, 1998; Kornack & Rakic, 1999). Previous research has shown that some newborn nerve cells are functionally recruited into the dentate gyrus and form appropriate synapses with already existing neurons (Cameron & McKay, 2001; van Praag et al, 2002). Ischemia causes damage to brain cells and can eventually lead to cell death. Recent studies on neurogenesis suggest that it may be possible for dead or injured neurons to be replaced (Liu et al, 1998; Jin et al, 2001; Zhu et al, 2003; Nakatomi et al, 2002). However, the molecular and cellular events underlying neurogenesis after cerebral ischemia are unclear.

The effects of oestrogen on cerebral ischemia has now been widely noticed. Oestrogen has been considered as a primary preventor of cerebral ischemia after menopause (Fan et al, 2003). It is suggested that ischemia-induced brain damage is concerned with the age of rats and the ischemic time. Additionally, there are many reports on the protective effects of oestrogen on ischemic rats (Wang et al, 2003; Alkayed et al, 1998). So far, the effects of oestrogen on ischemia-induced neurogenesis in the dentate gyrus has been rarely reported.

In the present study, we investigated whether cerebral ischemia-induced neurogenesis in the adult dentate gyrus was affected by oestrogen administration.

1　Materials and Methods

1.1　Animals

Thirty-two male adult Sprague Dawley rats (220－260 g body weight) were housed at standard temperature (22±3℃) with a 12 h light/dark cycle (lights on at 7:00). Free access to food and water was allowed.

1.2　Agents

Oestrogen (Sigma); BrdU (Sigma); 2,3,5-triphenyltetrazolium chloride (Sigma); Triton X-100; Rat monoclonal anti-BrdU (Sigma); Paraformaldehyde(Sigma); Normal goat serum (Sino-American biotechnology company); Antigen unmasking solution (Boster); Biotinylatedgoat anti rat IgG (Boster); The ABC kit (Vector laboratories); DAB kit (Vector laboratories).

1.3　Surgical preparation

Cerebral ischemia was induced by middle cerebral artery occlusion (MCAO), as described in Zhu et al (2003). With a rat under chloralhydrate anaesthesia (350 mg/kg), a round-tipped nylon monofilament was inserted into the right internal carotid artery (ICA) through the external carotid stump and pushed past the carotid bifurcation until a slight resistance was felt. Such resistance indicated that the filament had passed beyond the proximal segment of the anterior cerebral artery. At this point, the intraluminal filament blocked the origin of the MCA and occluded all sources of blood flow from the ICA, anterior cerebral artery and posterior cerebral artery. Throughout the procedure, body temperature was maintained at 37±0.5℃ with a thermostatically-controlled infrared lamp. The filament was left in place for 90 min and then withdrawn. The control rats were treated identically, except that the MCA was not occluded after the neck incision. Animals were then returned to their cages and carefully monitored until they recovered from anaesthesia.

1.4　Groups and treatment

Rats were assigned to four groups: the control surgery group with oestrogen administration (SE), the control surgery group with normal saline administration (SN), the MCAO group with oestrogen administration (ME), and the MCAO group with normal saline administration (MN).

1.5　BrdU and estrogen administration

Oestrogen was dissolved in 0.9% sterile saline and filtered. Rats of the SE and ME groups were injected with oestrogen (200 μg/kg, intraperitoneally) before ischemic injury. Rats of the SN and MN groups were injected with 0.9% sterile saline (1 mL/kg, intraperitoneally). All administrations were carried out once a day for 14 consecutive days.

Immediately after rats regained spontaneous respiration, they received an intraperitoneal injection of 50 mg/kg BrdU (Sigma) insterile 0.9% NaCl solution. The resulting solution was injected at 50 mg/kg (concentration of 10 mg/mL) in all rat groups after ischemia or control surgery. Rats received intraperitoneal injection of BrdU twice a day, with a 12 h interval between injections at 1, 3, 7, 14 and 21 days after MCAO, and were killed on the following day.

1.6　Determination of infarct volume

The infarct volume was determined in rats from the

experiments with ischemia or control operation as described in Zhu et al (2002). The brain was removed rapidly and chilled at −20℃ for 5 min. Coronal slices were made at 1 − 2 mm from the frontal tips, and sections were immersed in 2% 2,3,5-triphenyltetrazolium chloride (TTC) at 37℃ for 20 min. The presence or absence of infarction was determined by examining TTC-stained sections (Bose et al, 1984). Infarct volume was determined as described in Zhu et al (2002) and expressed as a percentage area of the coronal section in the infarcted hemisphere.

1.7 BrdU immunohistochemistry

Animals were perfused transcardially with 300 mL 0.05 mol/L sodium phosphate (pH 7.4) containing 0.8% NaCl, followed by 400 mL 4% paraformaldehyde in 0.05 mol/L sodium phosphate (pH 7.4, containing 0.8% NaCl). Their brains were removed and fixed overnight in the same solution. The whole brain was cut on a freezing microtome (Leica) and the 30 μm serial hippocampal sections were stored at 4 ℃.

BrdU staining has been described previously (Kim et al, 2004). The sections were heated (85℃ for 5 min) in antigen unmasking solution before being incubated in 2 mol/L HCl (30℃ for 30 min) and rinsed in 0.1 mol/L boric acid (pH 8.5) for 10 min. Then they were incubated in 1% H_2O_2 in phosphate-buffered saline (PBS) for 30 min, and blocked in PBS containing 3% normal goat serum, 0.3% (W/V) Triton X-100 and 0.1% bovine serum albumin (room temperature for 1 h). This was followed by incubation with rat monoclonal anti-BrdU (1∶200) at 4℃ overnight. Before incubation in the secondary antibody for 2 h at room temperature, sections were rinsed in PBS. After rinsing, the slices were treated with ABC solution for 30 min at room temperature. Sections were then processed using diaminobenzidine hydrochloride (DAB) as chromogen and mounted onto gelatin-coated slides and air-dried.

1.8 Nissl staining

Tissue sections adjacent to those used for immunohistochemistry were paraffin enveloped according to the routine way and stained to investigate histological damage caused by cerebral ischemia. Paraffin sections were mounted on gelatin-coated slides and deparaffinization, and then dipped in thionin for 5 to 7 min. Tissue sections were then differentiated in 70% acetic alcohol, dehydrated in ascending grades of alcohol, and cleared in dimethyl benzene.

1.9 Cell counting

Proliferating cells, detected by BrdU-positive nuclei, were counted by one experimenter who was unaware of the experimental conditions of each sample. The total number of BrdU-positive cells in the dentate gyrus was determined in eight coronal sections. The density of BrdU positive cells in each section was calculated by counting the number of BrdU positive nuclei and dividing by the area of the dentate gyrus according to the method of Liu et al (1998). Cell counts were expressed as the mean number of BrdU-positive cells per unit area (mm^2).

1.10 Statistical analysis

All data were presented as mean ± *SD*. Statistical analysis was performed using ANOVAs followed by a post hoc Tukey test and paired sample *t* test using the statistical software SPSS (Windows version 11.5). Differences were considered significant at $P < 0.05$.

2 Results

2.1 Pathological examination

A total of 32 rats were used for TTC staining. We found that, from 1.5 h after ischemia, the infarct volume gradually increases with time since reperfusion (Fig. 1). At each time point, the infarct volume of the ME group is significantly smaller than that of the MN group ($P < 0.05$).

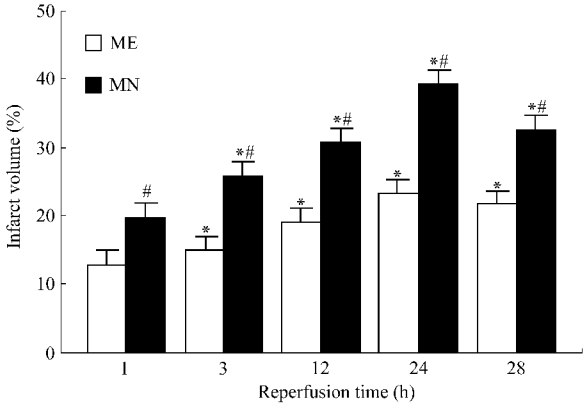

Fig. 1 Comparison of infarct volume at different times after MCAO

The number of rats used TTC staining in ME (MCAO + oestrogen) and MN (MCAO + Normal saline) are as follows: 1 h ($n = 6$), 3 h ($n = 6$), 12 h ($n = 7$), 24 h ($n = 6$), 28 h ($n = 7$). Data are expressed as mean ± *SD*; * $P < 0.05$, compared with rats after 1 h of MCAO in ME (MN) group; # $P < 0.05$, for MN group rats compared with ME group at the same time point (one-way ANOVA and paired sample *t* test).

2.2 Cell loss after ischemia

Analysis of Nissl-stained tissue sections revealed no cell loss in the control-operated animals and dramatic neuronal loss in ischemic rats. Ischemia-induced

neuronal loss largely involved the CA1 region (Fig. 2). Examination of ischemic tissues demonstrated a significant disruption in the neuropil and tissue vacuolization. These results underscore the fact that the CA1 region is selectively vulnerable to the effects of ischemia. Interestingly, our research showed that all cell loss occured only in the dorsal area of the hippocampus. No significant cell loss was seen in the ventral area of the hippocampus or in the dentate gyrus.

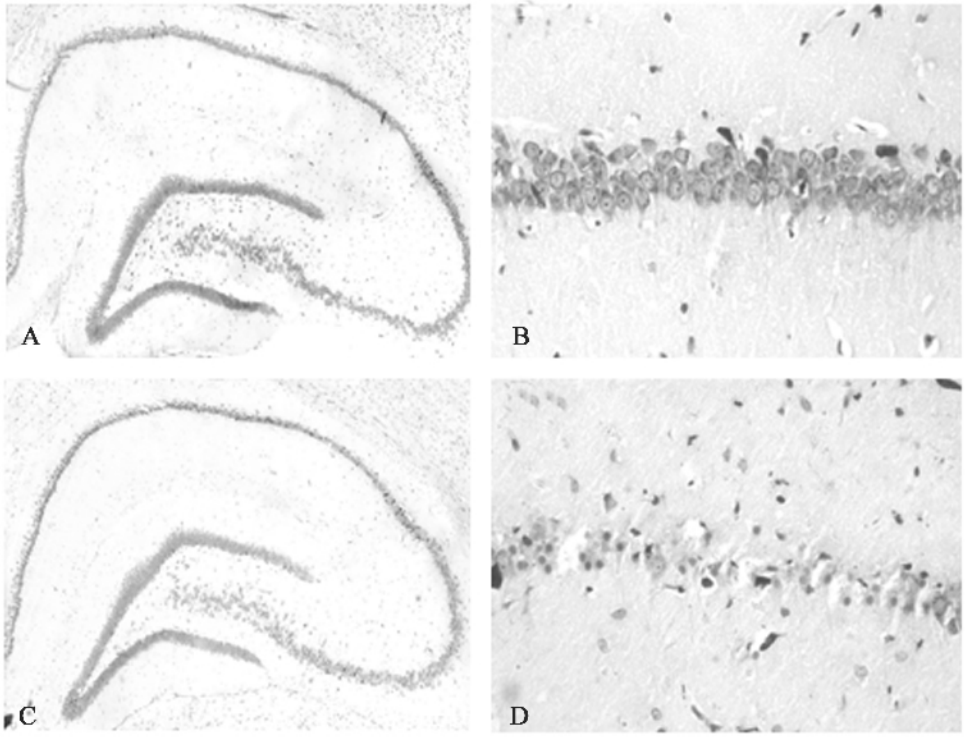

Fig. 2　Ischemia did not produce any cell loss in the dentate gyrus
Little cell loss was seen in control-operated animals (A and B), but distinct cell loss was found in ischemic animals (C and D), and neuronal cell loss was confined to the CA1 region of the hippocampus (B and D). Paraffin sections A and C: ×40; B and D: ×400.

2.3　Focal cerebral ischemia stimulates neurogenesis in the dentate gyrus

In one experiment, we determined whether focal cerebral ischemia could stimulate neurogenesis in the dentate gyrus and in the process of cell birth. As can be seen in Fig. 3, the basal level of BrdU-labeled cells in the dentate gyrus was unchanged in the control-operated animals or one day after MCAO, showing that the stress caused by surgery did not stimulate neurogenesis. However, the number of BrdU-positive cells started to increase three days after MCAO in the ipsilateral dentate gyrus but not in the contralateral dentate gyrus. Neurogenesis reached a peak seven days after ischemia and the number of BrdU-positive cells increased approximately four-fold compared with the controls. Although the number of BrdU-positive cells had decreased by day 14, it was still greater than that in the control surgery group. Neurogenesis in the dentate gyrus had declined to the basal level 21 days after MCAO.

2.4　Oestrogen leads to increased neurogenesis in the dentate gyrus

BrdU-positive cells were observed in the granule cell layer, subgranular zone, and hilus in all four groups (Fig. 4). The numbers of BrdU-positive cells in the ipsilateral dentate gyrus of the SN and SE groups were 123 ± 23 and 281 ± 32 mm^2, respectively. Those of the MN and ME groups were 644 ± 45 and 1 123 ± 104 mm^2, respectively. The numbers of BrdU-positive cells in the contralateral dentate gyrus of the SN and SE groups were 132 ± 20 and 291 ± 29 mm^2, respectively. Those of the MN and ME groups were 163 ± 31 and 325 ± 35 mm^2, respectively (Fig. 5).

BrdU-positive cells in the ipsilateral dentate gyrus of the MN group were increased compared with those of the SN group ($P < 0.05$, Fig. 5), while there was no

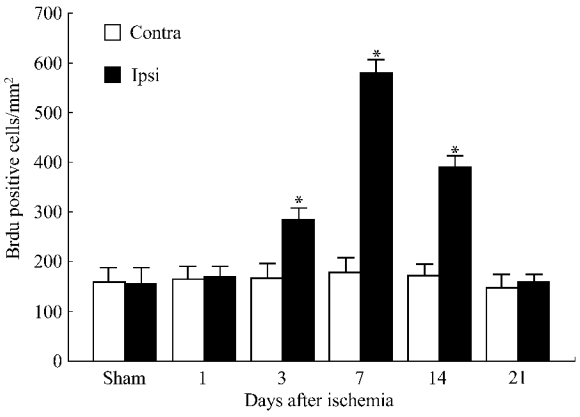

Fig. 3 Time course of neurogenesis in the dentate gyrus after MCAO

Rats received intraperitoneal injections of BrdU twice, with an 8 h interval between injections, after control operation ($n = 6$), or 1 day ($n = 4$), 3 days ($n = 6$), 7 days ($n = 6$), 14 days ($n = 6$), 21 days ($n = 4$) after MCAO. Rats were killed the following day. Contra: contralateral; Ipsi: ipsilateral. Data are mean ± SD, * $P < 0.05$ compared with controls (one-way ANOVA followed by post hoc Tukey test).

significant change in the contralateral dentate gyrus. This suggests that ischemia could lead to neurogenesis in the dentate gyrus.

At the same time, we found that BrdU-positive cells of the SE and ME groups in the ipsilateral dentate gyrus (Fig. 5) were increased compared with those of the SN and MN groups ($P < 0.05$). This is good proof that oestrogen can improve neurogenesis in the dentate gyrus. Interestingly, the number of BrdU-positive cells of the SE group in the contralateral dentate gyrus (Fig. 5) was also significantly increased compared with that of the SN group ($P < 0.05$). The results showed that oestrogen increased neurogenesis independent of ischemia induced damage in the dentate gyrus of rats.

3 Discussion

The observations in this study indicate that focal ischemic damage induced by MCAO leads to increased neurogenesis in the ipsilateral dentate gyrus. Oestrogen increased neurogenesis independent of ischemia induced damage in the dentate gyrus of rats. Direct and indirect evidence suggests that brain injury stimulates neurogenesis in the hippocampus (Gould & Tanapat, 1997; Jin et al, 2001; Yoshimura et al, 2001; Zhu et al, 2003, 2004). There is a precedent for oestrogen reducing ischemic infarct size (Horn et al, 2001). Oestrogen in the present study reduced infarct size, which is in agreement with many animal experiments and clinical trials, in which oestrogen shows a beneficial effect after cerebral ischemia (Horn et al, 2001).

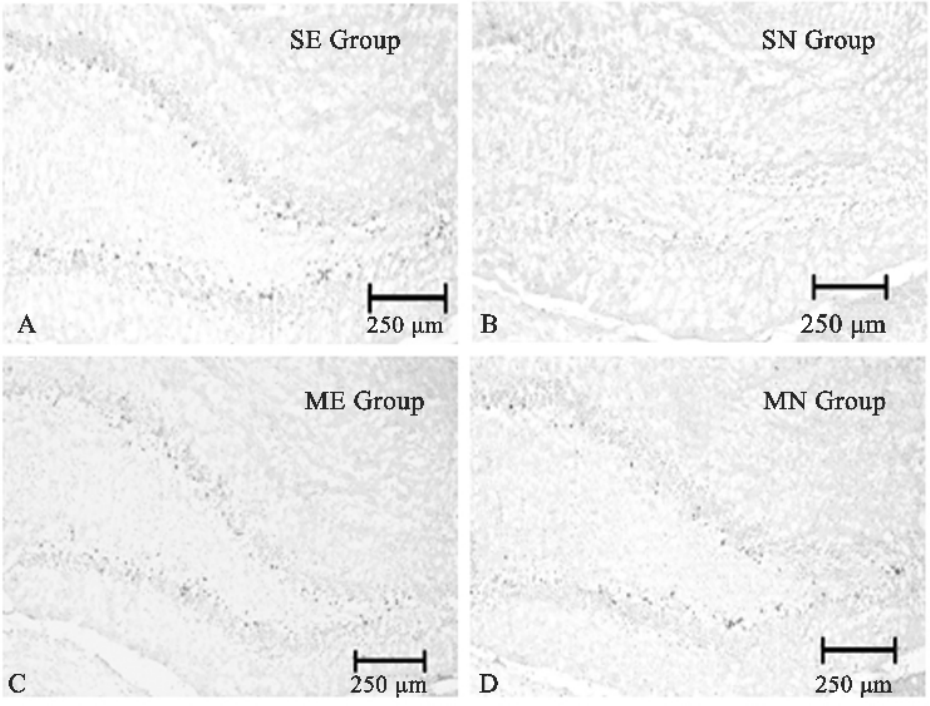

Fig. 4 The effects of oestrogen on ischemia-induced neurogenesis shown by representatives of BrdU labeling in the ipsilateral dentate gyrus of four groups (×40 magnification)

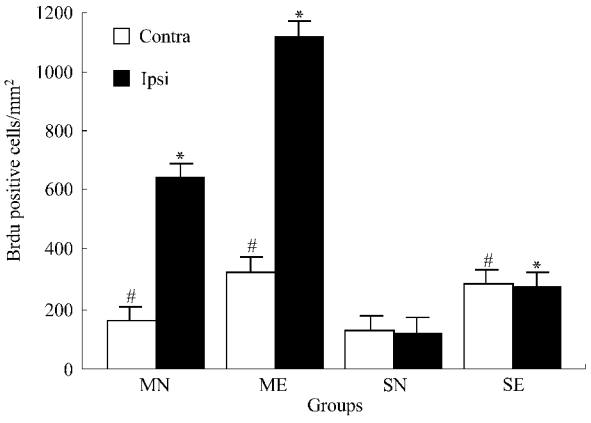

Fig. 5　The effects of oestrogen on ischemia-induced neurogenesis in the dentate gyrus, shown by the density of BrdU-positive cells in the four groups of rats ($n = 6$ animals in each group). Data are mean ± SD; * $P < 0.05$ compared with ipsilateral of the SN group; # $P < 0.05$ compared with contralateral of the SN group (one-way ANOVA followed by post hoc Tukey test).

In the present MCAO model, the data showed that there is no ischemia induced neuronal death in the dentate gyrus. We found that damage to the CA1 region, indicative of hippocampal ischemia, occurred in some animals seven days after MCAO, whereas cell birth is observed 3 – 4 days after MCAO. Furthermore, previous studies have certified that neurogenesis in the dentate gyrus after MCAO has nothing to do with the degree of cortex injury and loss of cortical neurons (Zhu & Auer, 1995; Zhu et al, 2003; Nakatomi et al, 2002). Together, these data suggest that increased neurogenesis from oestrogen after cerebral ischemia is independent of the extent of damage to the dentate gyrus. Thus, following ischemic damage, oestrogen is directly responsible for ischemia-induced neurogenesis in the dentate gyrus.

A recent study showed that inhibition of inducible nitric oxide synthase (iNOS) by pharmacological and genetic approaches prevents ischemia-induced neurogenesis(Zhu et al, 2003). With enhanced iNOS expression in the ischemic penumbra, it is demonstrated that there is a substantial increase in iNOS mRNA, iNOS protein content, iNOS activity and Nitric Oxide (NO) production in the dentate gyrus after cerebral ischemia (Zhu et al, 2002). It is well documented that oestrogen, as a general medicine in clinic, can lead to increased iNOS expression (Koyuncu et al, 2006). Thus we propose that increased neurogenesis, affected by oestrogen in the dentate gyrus after cerebral ischemia, is possibly due to increased expression of iNOS. It is worth further study to investigate whether there are any other factors regulating neurogenesis after MCAO.

In summary, although the possible pathways may vary, our results suggest that oestrogen promotes ischemia-induced neurogenesis in the dentate gyrus. Oestrogen might be a useful agent for the treatment of stroke and neurodegenerative disorders.

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王义权，男，1957 年 12 月生，厦门大学生命科学学院教授、博士生导师。1982 年毕业于安徽师范大学，学士；1985 毕业于陕西师范大学动物学助教班；1995 年毕业于南京师范大学动物学专业，博士；1997 年中国药大学博士后出站；1998 年 4—7 月香港科技大学访问学者；2000—2002 年美国德克萨斯大学访问教授、辛辛那提大学访问学者。目前兼任中国两栖爬行动物学会副理事长；福建省遗传学会常务理事；*Journal of Genetics & Genomics*、《遗传》、《动物学研究》编委等职。1982—1992 年于安徽师范大学从事动物学教学，主要从事两栖爬行动物的区系与生态学研究；1992—2002 年在南京师范大学读博士和工作期间主要从事两栖爬行动物的分子系统学和遗传多样性研究，2002 年 10 月于厦门大学生命科学学院主要从事文昌鱼的模式动物化及比较与功能基因研究。先后主持国家自然科学基金项目 3 项，国际交流项目 1 项，参加国家自然科学基金和国家“八五”攻关项目 3 项，另外主持省部级项目多项。在国内外发表研究论文 110 余篇，其中 SCI 收录期刊 19 篇；参编专著 5 部；获国家发明专利授权 1 项。目前在文昌鱼实验室人工养殖方面取得重要进展，解决了实验室条件下的人工繁殖难题，已获得了实验室子二代文昌鱼。