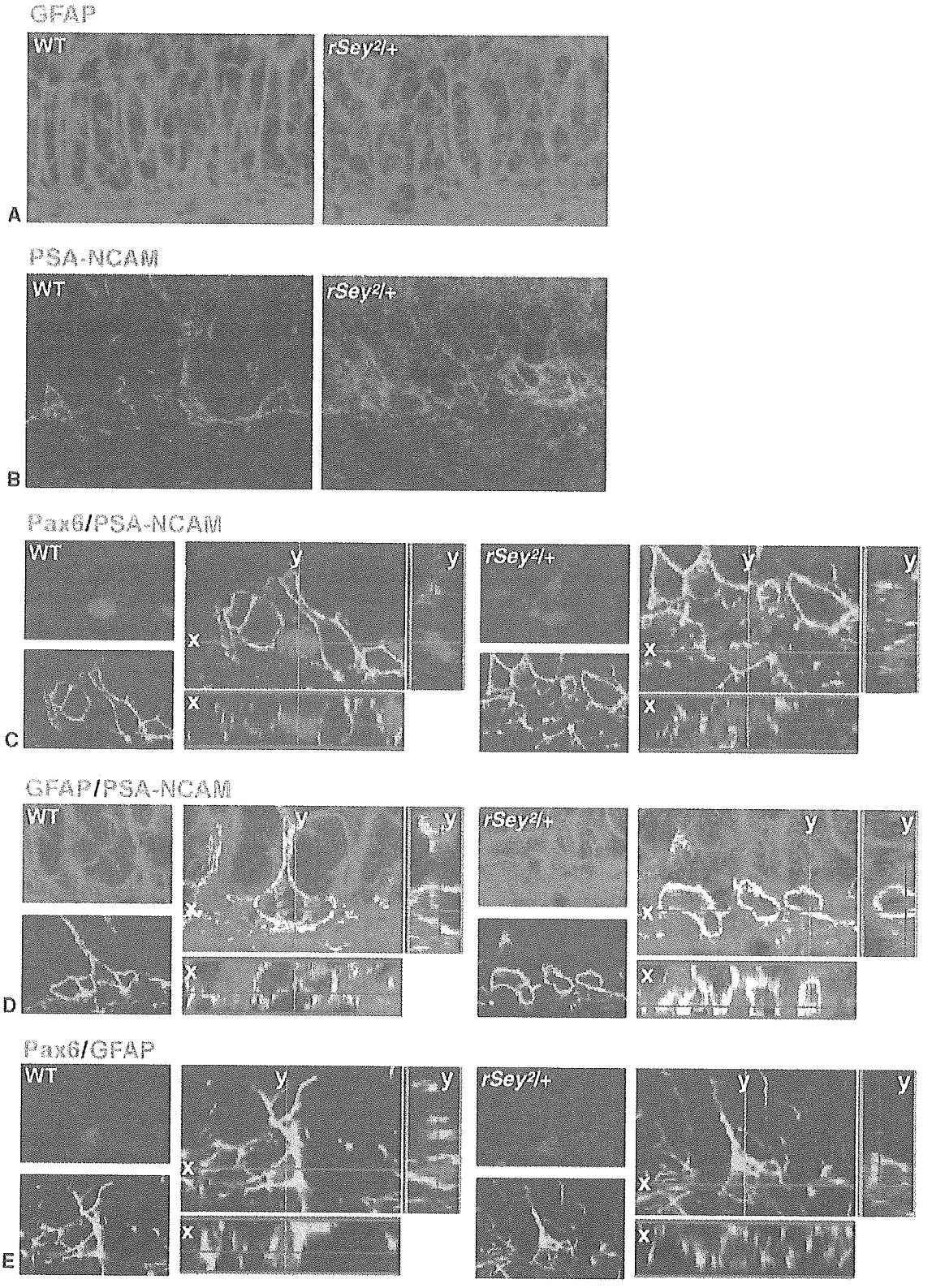

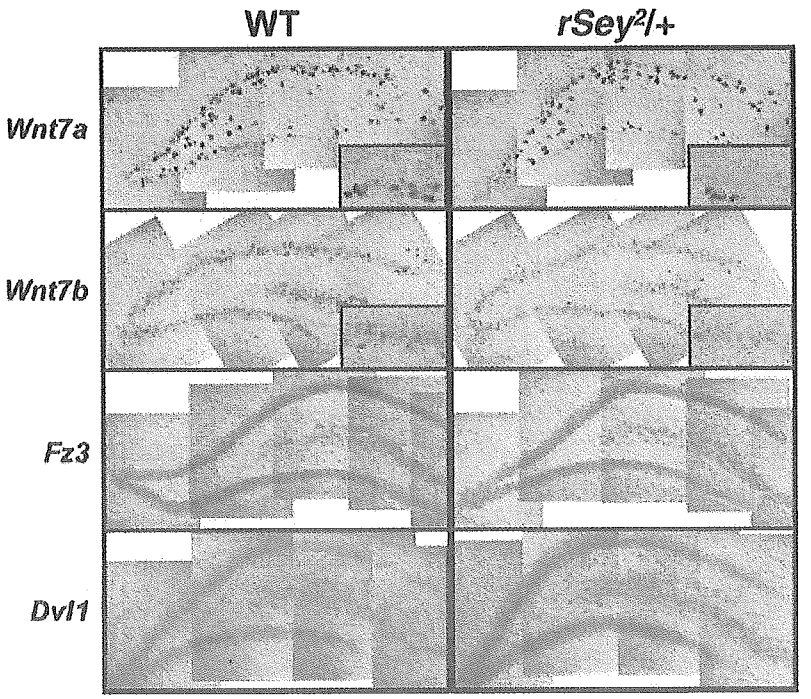


**Figure 6** Altered expressions of Wnt-signaling molecules in the DG of *rSey²/+*. In the hippocampus of wild-type, *Wnt7a* is expressed in the SGZ and hilus, while *Wnt7b*, *Fz3*, and *Dvl1* are expressed in the GL and SGZ. In the hippocampus of *rSey²/+*, the number of *Wnt7a*- and *Wnt7b*-expressing cells was decreased, and the expression level of *Wnt7b* was down-regulated. Contrastingly, the expression level of *Dvl1* was increased in the DG of *rSey²/+*. No difference between the wild-type and *rSey²/+* was observed in the expression level of *Fz3*.

process (Fig. 1C′), and Pax6$^+$/nestin$^+$ mostly showed a GFAP$^+$ early progenitor shape (Fig. 1B) and sometimes a PSA-NCAM$^+$ late progenitor cell shape. Pax6$^+$ cells sometimes co-expressed PSA-NCAM, but such Pax6$^+$/PSA-NCAM$^+$ cells always exhibited the late progenitor cell-like morphology. From immuno-electron microscopy, we found that the majority of Pax6$^+$ cells showed features corresponding to type B cells, and that a small number of Pax6$^+$ cells had characters corresponding to type D cells, while Pax6$^+$ cells never showed phenotypes of granule cells (Fig. 1D,D′, E,E′). Therefore, it is concluded that more than half of Pax6$^+$ cells have the character of the GFAP$^+$ early progenitor cells in the SGZ of the hippocampus (Fig. 7).

At present there are no good markers that properly distinguish quiescent neural stem cells from the progenitor cells in the hippocampal neurogenesis. However, we found that the ratio of BrdU$^+$ cells in Pax6$^+$ cells increased fivefold in a 2-week BrdU labeling compared to that in a 30-min labeling. It is thus likely that a population of Pax6-expressing cells may include the quiescent neural stem/progenitor cells in the hippocampus.

**Figure 5** Abnormal PSA-NCAM$^+$ cells and GFAP$^+$ cells in *rSey²/+* rats at 4 weeks. (A) In *rSey²/+* rats, there are fewer GFAP$^+$ cells whose processes are thin and underdeveloped. (B) PSA-NCAM$^+$ cells are increased in number and abnormally colonized at the SGZ in *rSey²/+* rats. (C) In the wild-type (WT) rat, PSA-NCAM$^+$ cells scarcely co-express Pax6. Contrastingly, many Pax6$^+$ cells co-express PSA-NCAM in *rSey²/+* rat. In *rSey²/+* rat, Pax6 expression is down-regulated comparing with WT. (D) In the WT rat, PSA-NCAM$^+$ cells scarcely co-express GFAP. Contrastingly, many PSA-NCAM$^+$ cells co-express GFAP in *rSey²/+* rat. (E) In the WT and *rSey²/+* rats, a GFAP$^+$ radial glial cell co-expresses Pax6. In the *rSey²/+* rat, a process of the GFAP+ radial glial cell is thin and undeveloped, and the expression of Pax6 is reduced.

### The role of Pax6 in postnatal hippocampus

As discussed above, Pax6$^+$ cells have the character of neural stem cells and GFAP$^+$ early progenitor cells in the DG of postnatal hippocampus. It is thus expected that Pax6 is involved in cell proliferation and/or cell differentiation in hippocampal neurogenesis.

There are some papers where Pax6 is involved in cell proliferation in developing cortex (Warren *et al.* 1999). We found from BrdU labeling analyses that cell proliferation was dramatically reduced in the *Pax6*-deficient DG (Fig. 2A). In addition, more than 90% of total BrdU$^+$ cells were Pax6-positive at 30 min after BrdU injection in the SGZ of adult hippocampus (Fig. 4A,B). These data

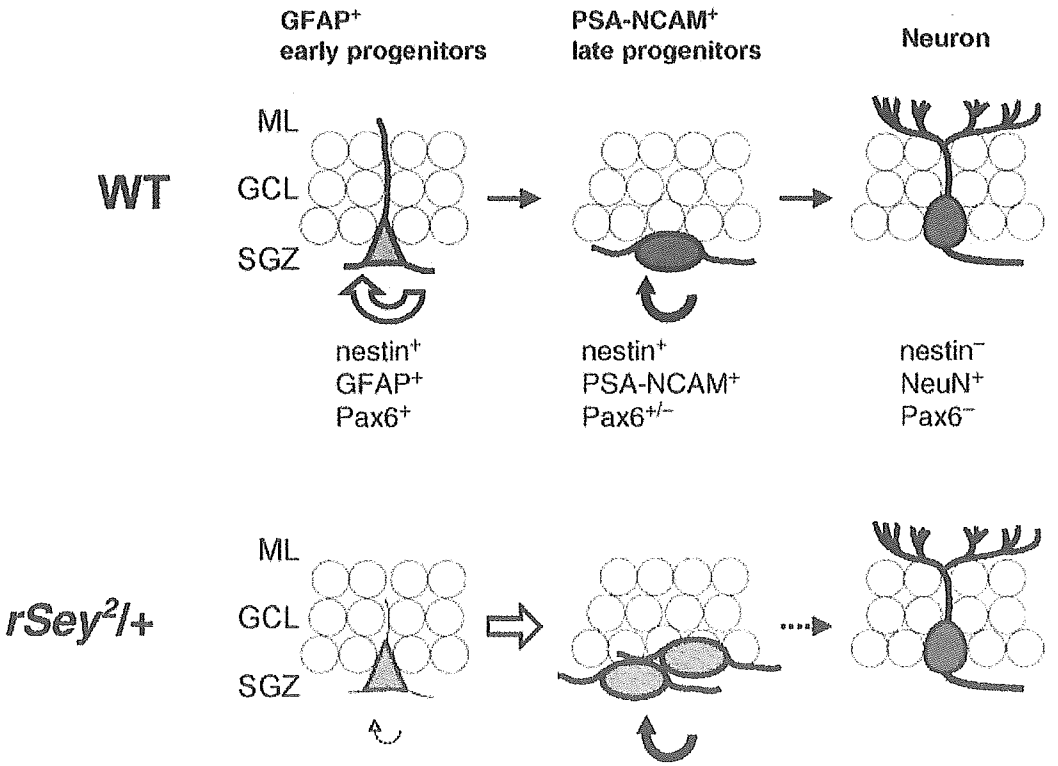


**Figure 7** The role of Pax6 in adult hippocampal neurognesis. Distinct progenitor cells are identified on the basis of morphology, proliferative activity, and marker expressions. In the wild type (WT), GFAP$^+$ early progenitors have a radial glial appearance with the cell body in the subgranular zone (SGZ) of the dentate gyrus, and also express nestin and Pax6. PSA-NCAM$^+$ late progenitors have plump short processes that are oriented tangentially, and they are nestin$^{+/-}$, GFAP-, PSA-NAM$^+$ and Pax6$^{+/-}$. Mature neurons in the granule cell layer (GCL) retain a vertical morphology with a rounded or slightly triangular nucleus and clearly visible apical dendrites, and they are nestin$^-$, Pax6$^-$, and NeuN$^+$. In *Pax6* deficient condition (*rSey*$^2$/+), GFAP$^+$ early progenitors have a thinner and undeveloped radial process and are fewer in number than in the WT. There is a more rapid shift from the GFAP$^+$ early progenitor cells to the PSA-NCAM$^+$ late progenitor cells in *rSey*$^2$/+ (big arrow). These PSA-NCAM$^+$ late progenitors show abnormal morphology, ectopic location, and altered molecular character (i.e. increased PSA-NCAM$^+$/Pax6$^+$ and PSA-NCAM$^+$/GFAP$^+$ double positive cells). That is, production of the early progenitor cells is impaired in *Pax6* deficient condition, thereby generating fewer neurons (dotted arrow).

strongly suggest that Pax6 is vital for the cell proliferation in the hippocampal neurogenesis. Then, for which steps of the neurogenesis is Pax6 required in cell proliferation?

Previous papers report that both GFAP$^+$ early progenitor cells and PSA-NCAM$^+$ late progenitor cells are transit amplifying cells. Rapid transition from GFAP$^+$ early progenitors/type B cells to PSA-NCAM$^+$ late progenitors/type D cells occurs between 2 and 24 h after the BrdU single injection (Seri *et al.* 2001; Fukuda *et al.* 2003). In the similar experiment, we found dramatic decrease in the number of GFAP$^+$/BrdU$^+$ cells and an inverse increase in the number of PSA-NCAM$^+$/BrdU$^+$ cells in the SGZ of the *rSey*$^2$/+ (Fig. 4C,D). Moreover, the morphology of GFAP$^+$ cells was altered in *rSey*$^2$/+ (Figs 2C′, 5A, 5E). Our findings suggest that the maintenance of the GFAP$^+$ early progenitor cells is perturbed in the DG of the *rSey*$^2$/+, presumably resulting in a more rapid shift from the GFAP$^+$ early progenitors to the PSA-NCAM$^+$ late progenitors (Fig. 7).

There are some reports that Pax6 promotes neuronal differentiation in the developing cortex and adult SVZ (Heins *et al.* 2002; Hack *et al.* 2004, 2005). To test the possibility that Pax6 is involved in neuronal differentiation in the postnatal hippocampus, we examined the ratio of NeuN$^+$/total BrdU$^+$ cells at 5 days time point after the BrdU injection in *rSey*$^2$/+. The ratio of NeuN$^+$/BrdU$^+$ cells in *rSey*$^2$/+ was not different from that in the WT, even though there is a more rapid shift from the

GFAP$^+$ early progenitor cells to the PSA-NCAM$^+$ late progenitor cells in *rSey²/+*. Therefore, such abnormally differentiated PSA-NCAM$^+$ late progenitor cells did not effectively contribute to produce neurons. In fact, these PSA-NCAM$^+$ late progenitor cells exhibited abnormal characters; they often retained GFAP expression, which is hardly observed in the WT, and did not line up at the SGZ but colonized in disorganized positions (Fig. 5B,D). Since we observed increased cell death in *rSey²/+* (M.M. and N.O., unpublished observation), such functionally abnormal PSA-NCAM$^+$ late progenitor cells may eventually die off in the SGZ of the *rSey²/+*. Taken altogether, Pax6 functions in cell proliferation rather than differentiation in the DG.

We found a marked decrease of the percentage of GFAP$^+$ in BrdU$^+$ cells in *rSey²/+* compared with the wild type, while no significant difference was detected in the percentage of NeuN$^+$ in all BrdU$^+$ cells at 4 weeks after the BrdU injection (Fig. 3C,D). However, since the total number of BrdU$^+$ cells dramatically decreased in *rSey²/+*, newly generated granule cells were markedly reduced in *rSey²/+* rat. Eventually, at 16 weeks, the GCL became thinner in the DG of *rSey²/+* rats than that of the wild type (Fig. 2B). Therefore, it is suggested that Pax6 primarily functions to maintain the progenitor pool in the hippocampus; if the size of the progenitor pool is reduced by Pax6 haplo-insufficiency, the subsequent production of neurons is severely impaired.

The number of Pax6$^+$/GFAP$^+$ cells, BrdU$^+$ cells (BrdU labeling three times a day for 3 days) and BrdU$^+$/Pax6$^+$ cells (BrdU labeling two times a day for 2 weeks) were already more reduced in *rSey²/+* rats than in WT rats at the earliest time point we observed (4 weeks). Therefore, it is possible that Pax6 is necessary for the production of GFAP$^+$ early progenitor cells during the initial formation of the hippcampus. This is quite reasonable because we observed that extremely less GFAP$^+$ cells (including not only those mature astrocytes but also neural stem/progenitor cells) were produced in the DG of *rSey²/+* rats (Fig. 3C,D). Taken all together, it is concluded that Pax6 is necessary for keeping a good balance between cell proliferation and differentiation in the hippocampal neurogenesis (Fig. 7).

### Pax6–Wnt pathway in hippocampal neurogenesis

Because Pax6 is a transcription factor, its influence on the production of GFAP$^+$ early progenitor cells is naturally brought by transcriptional regulation of other genes. Although several secreted molecules such as EGF, FGF2, BDNF, and Shh have been known to regulate adult neurogenesis (Craig *et al.* 1996; Kuhn *et al.* 1997; Tropepe *et al.* 1997; Zigova *et al.* 1998; Machold *et al.* 2003), we could not find any difference in expression of these molecules in the DG of *rSey²/+* rats (not shown). However, we have found dramatically different expression patterns of genes involved in Wnt signaling pathway.

Wnt genes encode secreted proteins that regulate fate decisions of various cells depending on the context. The functions of Wnt signaling are studied intensively in many aspects of embryogenesis such as anterior–posterior axis formation, cell type specification, cell proliferation, and axonal growth (Patapoutian & Reichardt 2000; Wang & Wynshaw-Boris 2004; Zou 2004). Although Wnt signaling in the postnatal brain has been comparatively little investigated, a recent report describes remarkably patterned gene expressions of Wnt signaling components in the postnatal mouse brain including the hippocampus (Shimogori *et al.* 2004). In addition, Wnt signaling has already been reported to be altered in embryonic brains of *Pax6* mutant mice and rats (Grindley *et al.* 1997; Osumi *et al.* 1997; Warren & Price 1997; Kim *et al.* 2001; Takahashi *et al.* 2002). We found specific expression of *Wnt7a* and *Wnt7b* in the wild-type SGZ, and marked reduction of *Wnt7a* and *Wnt7b* expressions in the DG of the *rSey²/+*. Conversely, *Dv1* was up-regulated in the DG of the *rSey²/+* (Fig. 6). Therefore, Wnt signaling is altered in the *Pax6*-deficient DG.

During cortical development, Wnt signaling has multiple and stage-specific roles. In early embryonic stages, Wnt7a, 7b, and stabilized β-catenin promote self-renewal of neural precursor cells and suppress neural differentiation (Chenn & Walsh 2002; Viti *et al.* 2003). On the other hand, it is reported that the Wnt/β-catenin pathway directs neuronal differentiation of the cortical precursor cells at later developmental stages (Hirabayashi *et al.* 2004). Curiously, in adult hippocampus, lithium facilitates proliferation and differentiation of progenitor cells to a specific neural cell type by perturbing functions of GSK3β, a pivotal player not only in the PI3 kinase pathway but also in Wnt/β-catenin pathway (Chen *et al.* 2000; Kim *et al.* 2004). In the present study, we found that specific expressions of Wnt ligands in the SGZ and that Wnt signaling is altered in the DG of *Pax6*-deficient rat (Fig. 6) suggest an intriguing possibility that impaired Wnt signaling may perturb the production of GFAP$^+$ early progenitor cells in postnatal hippocampus. Expression patterns of *Wnt7a* and *7b* may also support the idea that cells expressing Wnt ligands constitute an environment as a stem cell niche to maintain neural progenitor cells. It would be important to elucidate how Pax6–Wnt signaling coordinately regulates proliferation of neural stem cells/GFAP$^+$ early progenitor cells in the SGZ.

## Experimental procedures

### Animals

Large colonies of heterozygous *Pax6* mutant rats (*rSey²*/+) and wild-type Sprague–Dawley (SD) rats (littermates of *rSey²*/+ rats) were maintained at Tohoku University School of Medicine and National Institute of Neuroscience. The genotype of *rSey²*/+ rats was distinguishable based on the presence of eye defects. All animal experiments were carried out in accordance with the National Institute of Health guidelines for the care and use of laboratory animals and were approved by the Committee for Animal Experiments in the aforementioned organizations.

### Tissue preparation

Rats were deeply anesthetized with diethyl ether or pentobarbital sodium before sacrifice. Brains were perfused transcardially with 4% paraformaldehyde (PFA) in 0.01 M PBS (sodium phosphate buffer, pH 7.4) or 4% PFA and 0.5% picric acid in 0.01 M PBS, or 2% PFA and 2.5% glutaraldehyde in 0.01 M PBS, for immunohistochemistry, immuno-electron microscopic analysis, and conventional electron microscopic analysis, respectively. The brains were incubated in the same fixative for 2 h at 4 °C and cut into 70 μm coronal sections with a vibratome (Leica) or cut by a cryostat (Leica) into 14 μm sagittal sections.

### Immunohistochemistry

Procedures were basically according to the previous reports (Osumi *et al.* 1997; Fukuda *et al.* 2003). Detailed information will be provided on request. Antibodies against Musashi, nestin, and PSA-NCAM are kind gifts from Drs Hideyuki Okano, Masaharu Ogawa, and Tatsunori Seki (Miyata & Ogawa 1994; Seki & Arai 1999; Kaneko *et al.* 2000). Fluorescent signals were detected using a confocal laser-scanning microscope (Leica) or a fluorescent microscope (Axioplan-2, Zeiss).

### BrdU labeling analyses

Four-week-old rats received single intraperitoneal injections of 5-bromo-2-deoxyuridine (BrdU) (Sigma, St. Louis, MO) at 50 μg/kg body weight (10 mg/mL stock, dissolved in 0.9% saline), and were sacrificed at 30 min, 24 h, and 72 h after the injection (Seri *et al.* 2001; Kempermann *et al.* 2004). For cell fate analyses, 4-, 12- or 20-week-old rats received similar injections of BrdU three times a day for 3 days, and were sacrificed at day 1 or 4 weeks later (Kempermann & Gage 1999). For quiescent stem cell analysis, 4-week-old rats received injections of BrdU twice a day for 14 days, and were sacrificed 1 day later (Magavi *et al.* 2000). Seventy micrometers free-floating sections were cut and incubated in 2 N HCl for 1 h at room temperature, and washed in 0.01 M PBS (Saegusa *et al.* 2004). Otherwise, 14 μm frozen sections were boiled in 0.01 M citric acid and incubated in 2 N HCl for 10 min at 37 °C, and washed in 0.01 M PBS.

### Quantification

For BrdU pulse/chase examination, percentages of $Pax6^+$, $GFAP^+$, or PSA-$NCAM^+$ in total $BrdU^+$ cells were calculated in three sections per hemisphere. For quantification analysis, sampling of BrdU-positive cells was performed throughout the DG in its rostrocaudal extension. Every sixth section (14 μm) was used for counting, and the total number was obtained by multiplying the value by 6 (Kempermann & Gage 1999). For the fate analysis, $BrdU^+$/$NeuN^+$ in total $BrdU^+$ cells and $BrdU^+$/$GFAP^+$ in total $BrdU^+$ cells were counted in three adjacent sections in the same rostrocaudal regions of a DG (Kempermann & Gage 1999). For the quantification of the number of $GFAP^+$/$Pax6^+$ double-positive cells and $Pax6^+$/$BrdU^+$ double-positive cells, we counted these cells within the limited range in six adjacent sections and calculated the density. The number of these cells was counted in the blind manner.

### Electron microscopy

Procedures were basically according to the previous reports (Yuasa *et al.* 1996; Saegusa *et al.* 2004). Detailed information will be provided on request. These ultrathin sections were stained with lead citrate and uranyl acetate, and observed under a Hitachi H-7000 electron microscope.

### *In situ* hybridization

Procedures were basically according to the previous reports (Osumi *et al.* 1997; Takahashi *et al.* 2002). *Wnt7a*- and *Wnt7b*-expressing cells were counted on three adjacent sections in the same rostrocaudal region of a DG.

### Statistical analysis

Statistical analyses were performed with Microsoft Excel (Office 98), and ANOVA or two-sided *t*-test was applied when appropriate.

## Acknowledgements

We thank Drs Kazunobu Sawamoto, Tatsunori Seki, Toshiya Manabe, and Fiona Doetsch for the kind exchange of unpublished results and discussions and Drs Hideyuki Okano, Masaharu Ogawa, and Tatsunori Seki for valuable antibodies. We are also grateful to Drs Yoshiro Toyama and Yoshinichi Kozuka for the advice and support on the electron microscopic observations. We also thank Ms. Michi Otonari and Hisako Yusa for maintenance of the *rSey²* rat colony, and Ms. Yumi Watanabe for technical assistance. This work was supported by grant-in-aid #16047202 for Scientific Research on Priority Areas from the Ministry of Education, Culture, Sports, Science and Technology of Japan, and Japanese Science and Technology Corporation given to N.O., T.N., and K.I.

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*Received*: 13 March 2005
*Accepted*: 11 July 2005

*The Japanese Journal of Psychonomic Science*
2005, Vol. 24, No. 1, 119–120

**Summary of Awarded Presentation** **1P48**

# Cue availability changes the orbitofrontal activation for olfactory stimuli

## —A NIRS imaging study—

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Some studies have reported that the orbitofrontal cortex (OFC) increases its activation relative to the intensity of an olfactory stimulus. On the other hand, some studies have suggested that this phenomenon is not observed. The procedural difference of the 2 groups of investigations was the concurrent presentation, or not, of an additional cue. Our study focused on this difference and involved a neuro-imaging technique to investigate the effects, on 6 participants, of a verbal cue and changes of olfactory stimulus intensity. We observed that when the verbal cue was absent, activation of the OFC was related to the stimulus intensity. This result was in agreement with the observations of previous studies. However, although activation of the OFC is linearly related to the intensity of the olfactory stimulus when other cues are present this linear relationship may become unclear.

**Key words**: olfaction, orbitofrontal cortex, near-infrared spectroscopy

### Introduction

Several neuro-imaging studies suggest that the orbitofrontal cortex (OFC) is a higher center for processing olfactory stimuli. However, the OFC is considered to play various roles, not only for olfactory sensory processing but also for accommodating adaptive behavior. Thus there is some disagreement about the reason for activation of the OFC when this is evoked by olfactory stimulation. Although some studies have suggested that OFC activation (the amount of blood flow) would increase relative to olfactory stimulus intensity, other studies have reported that the stimulus intensity did not have an effect on the amount of activation. In some neuro-imaging studies which have measured the activation of the OFC evoked by olfactory stimuli, there have also been vocal, visual, or haptic cues concurrently presented. However, because the OFC is involved in associative learning, the use of these cues might mask any effects of changing the stimulus intensity. Indeed, an intensity effect was observed in a study in which concurrent cues were not used (Rolls, Kringelbach, & de Araujo, 2003). However, the effect has not been observed in studies in which have used these cues (Royet, Hudry, Zald, Godinot, Gregoire, Lavenne, Costes, & Holley, 2001; Anderson, Christoff, Stappen, Panitz, Ghahremani, Glover, Gabrieli, & Sobel, 2003). In the present study, we investigated the effects of olfactory stimulus intensity and presentation of a concurrent cue on activation of the OFC.

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### Method

**Participants** The participants were 6 graduate and undergraduate students of Hiroshima University. All of the students had normal olfaction and were right handed. Their average age was 23 years.

**Materials** We used γ-undecalacton, which has a matured peach-like smell, from a standardized olfactory stimulus set (Daiichi Yakuhin Industrial, Tokyo, Japan) to manipulate the intensity of the olfactory stimulus. Near-infrared spectroscopy equipment (ETG-100, Hitachi Medical, Tokyo, Japan) was used to measure the amount of blood flow in the or-

bitofrontal cortex.

**Procedure** The participants were instructed to breathe naturally and keep their eyes closed. The olfactory stimuli were presented 3 times for each of the strong and weak conditions by bringing a filter paper impregnated with γ-undecalacton to within approximately 2 cm of a subject's nose. Each presentation was for 15 seconds, and this was followed by 30 seconds of rest. In one condition a concurrent verbal cue was presented. In the other condition the verbal cue was not presented. The order of presentation of the olfactory stimulus intensity and the verbal cue was counterbalanced between participants. Seven measurement points (channels) on the forehead of a each participant were used to investigate their OFC hemodynamics (oxy-Hb)., The position of these channels, according to the international 10–20 method, covered the OFC region (see Figure 1). The sampling rate was 0.5 seconds.

## Results

We calculated the average oxy-Hb values from 3 to 10 seconds after the stimulus onset, and used these values in our analysis. We then used a two-way ANOVA, with the stimulus intensity (strong, weak) and the verbal cue (presented, not presented) , both as within-subject factors. The results indicated significant interactions in channel 1 ($F(1, 5)=7.439$, $p<0.05$) and channel 5 ($F(1, 5)=6.892$, $p<0.05$).

## Discussion

The results revealed that when the verbal cues were not presented, activation of the OFC was linear with the stimulus intensity. On the other hand, when verbal cues were presented, activation of the OFC was not observed. It is suggested that when verbal cues were presented the participants may have used this information, which was more salient than the olfactory stimuli, and therefore activation of the OFC was not observed. Consequently, the results indicate that activation of the OFC reflects processing of the intensity of an olfactory stimulus.

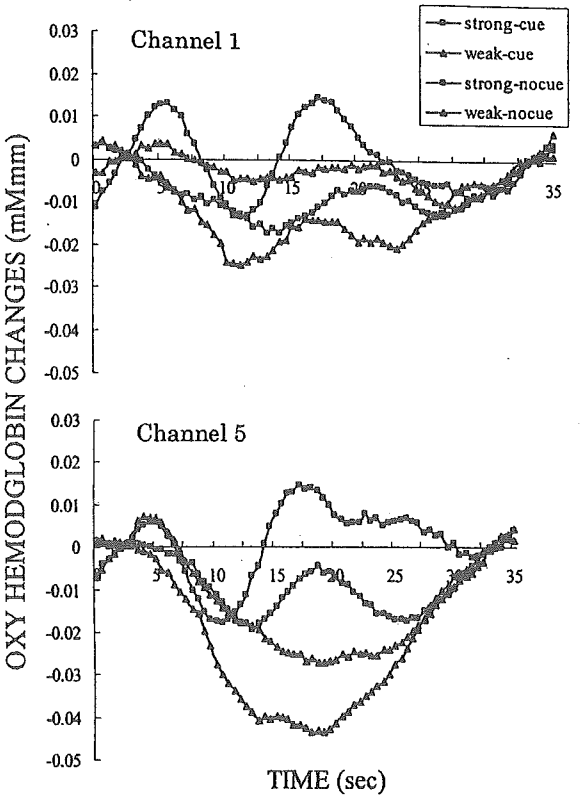


Figure 1. Oxy hemoglobin changes for stimulus intensity (strong/weak) and cue availability (cue/nocue) in channel 1 (upper) and 5 (lower).

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# 発達障害と児童虐待（Maltreatment）

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『子どもの虐待とネグレクト』第7巻3号
（2005年12月20日発行）より別刷

特集2■発達障害と児童虐待

# 発達障害と児童虐待（Maltreatment）

田中　康雄 (1)

## はじめに

「発達障害と児童虐待（Maltreatment）」というテーマは、それ自体ひじょうな難しさを持っている。こうして並記することが、すでに何らかの因果関係や関連を自明のこととしているかのようであるが、当然これらが証明されているわけでもなければ、発達障害のある子どもの多くが虐待されているという確証もない。

しかし、なぜこのようなテーマが求められているのだろう。

ささやかな経験であるが、私は虐待を受けて育った子どもたちに、病院の診察室や保護されている施設で出会う。そこで診る子どもたちは、あたかも発達障害がすでにあったかのような言動を示す場合が少なくない。一方で、発達障害のある子どもたちの面接場面に同席する養育者の言動に不適切な関係を読み取る場合もある。日々の臨床場面から、虐待（Maltreatment）は、なにかしら子どもの発達を阻害する大きな要因と呼べるのではないだろうかと仮定してみたり、発達障害の存在は、子どもへの向き合い方それ自体を困難にするのではないだろうかと、思わされたりする。ところが、このニワトリが先か卵が先かの論争は、果たしてその卵はニワトリの卵かという根本的な部分からつまずいている。

改めて、この両者の位置づけについて再検討するのが、本論文の目的である。はじめに断っておきたいが、検討のなかで、あたかも養育者の態度が、発達障害を生むかのような印象を読者に抱かせるようなことがあれば、単純に私の筆力不足である。私は子どもの発達に影響を与える要因は様々であり、虐待（Maltreatment）の誘因も重層化しているものという理解に立つことを明らかにしておきたい。

## 虐待（Maltreatment）が発達に与える影響

本文では、虐待（Maltreatment）と表記する。本来、児童虐待という用語には、虐待（Abuse）と放任（Neglect）という両極の子どもへの対応という意味が含まれている[19]。しかし、児童虐待という表記からは、放任がどうしてもイメージされにくい。常時「児童虐待と放任」と表記する方法もあるが、今回のテーマには、大人と子どもの関係性を重視するという視点[5]が不可欠のように思われる。そのため、「不適切な養育」と訳されることの多いMaltreatmentという用語を付記し、虐待（Maltreatment）と表記することにした。

子どもの発達に影響を与える要因を、Mussenら[17]は5つに分類した（表1）。それによると、虐待（Maltreatment）が発達に与える影響は、4）の直接の社会的・心理的影響を主に、5）の

Developmental disorders and maltreatment
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表1　発達に影響する要因

| |
|---|
| 1）遺伝的に決定された生物学的要因 |
| 2）非遺伝的な生物学的要因 |
| 3）子どもの過去における学習 |
| 4）直接の社会的・心理的影響 |
| 5）その中で子どもが育つ総体的な社会的・文化的な環境 |

総体的な社会的・文化的な環境を従としているように思われる。

1952年に、乳幼児期における母性的養育は、精神の健康にとって不可欠であると主張したBowlbyは、少ない事例研究ではあるが、「施設で育てられた子どもたちの発達は概して悪く、言語の習得が遅れ、成長するにつれて他者との安定した人間関係を形成する能力を欠く」という結論を得た。これは、同じくBowlbyの「悪い家庭といえども良い施設に勝る」という言葉とともに、ある意味先駆的な見解といえるかもしれない[9]。

実際には、Bowlbyの発見の前の1934年にHildegardら[28]は、入院した子どもの様子を観察し「献身的で愛情に満ちた母親に世話されることで、子どもが元気になる」ことを明確にした。1945年にSpitz[23]は、同様の現象を深刻な事態として強調した形で「ホスピタリズム」という用語を用いて報告した。Spitzは、愛情の欠如を経験した子どもは、事実上例外なく落伍者になるといい、ホスピタリズムの影響として「非社交性、犯罪行為、精神薄弱、狂気、神経症が例外なく認められる」とした。現代から読み直すと、ひじょうに扇動的で社会的な不安を駆り立てる意見である。しかし、1938年に、すでにMargaretは、「自分をよく受けいれてくれない母親に対して、一時的な呼吸停止を示した」新生児の事例を報告している[23]。これも強い印象を与える報告といえよう。

われわれがよく知るところでは、1958年にHarlowによるアカゲザルの報告がある。出産直後に母子分離されたアカゲザルは、代償的に差し出された針金製のあるいは布製の代理母親にしがみついた。次に針金製の母親にミルクを取り付け、布製のほうにはなにも取り付けなくとも、アカゲザルは布製の母親を好む、という結果を得た。さらに、しがみつくものもないままに孤立した状況で育てられると、成長後に情緒的混乱と抑うつの徴候を示したという。

近年こうした観察実験から得た過去の知見を、脳科学的視点あるいは精神生物学的な見解から読み解こうとしている。実際、虐待（Maltreatment）が発達に与える影響として、成長障害[11]や、運動、言語、認知力の遅れ[16]、不注意、多動性[13]、社交性の欠如[12]、愛着性障害[18]、さらに自閉症類似の言動（autistic-like behaviors）[2]などの状態像が示唆されてきている（表2）。これは、環境が脳の発達に対し、なにかしらの影響を与えるという仮説の支持に役立っている[8]。

環境を前提にした研究として、1980年、Belskyら[3]は親と子どもの特性と社会的・文化的要因、家族状況を視野に入れた環境相互作用モデルを作成した（図1）これは、支援策を考える時にひじょうに役立つ。育てる者と育てられる者との間に生まれる関わりを養育（Parenting）と呼ぶとき、それは、親のこれまでの育ちの歴史から育まれた親のパーソナリティと子どもの発達状況や子どもの示す言動との相互の交わりから生まれる。しかし、この両者を支えあるいは追いつめる要因として、夫婦・家庭状況や、仕事・経済状況、社会的ネットワークといったものが重要な役割を果たすというわけである。

一方、De Bellis[7]は、ネグレクトによる精神生物学的見地からの発達性外傷学（Developmental Traumatology）を提唱している（図2）。これは、生物学的視点から、相互関係性について明示したものである。

子育ての領域では、虐待（Maltreatment）と親の精神的病状や薬物の乱用を危険因子として挙げている。環境の領域では、Belskyにならい生態学的見地に立ち、社会経済的地位、栄養状態、コミュニティや社会からの支援、家庭内暴力、教育機会の付与などを重視している。

Belskyにない視点として、De Bellisは以下のよ

うな項目を検討した。神経伝達物質や免疫機能の失調として認められる生物学的なストレスの調整不全や前頭前頭野機能や辺縁系機能の異常、神経認知機能のつまずきとしての知能指数の低値、学習能力不全、ネグレクトの世代間伝達、遺伝因子などをそれぞれ危険因子とした。一方で、弾性力としての健全な脳の機能的発達にも注目している（図2）。

1900年代初め、小児科医による入院幼児の成長障害と感染による死亡率の高さが報告された。いずれも社会的理由により養育者から離別した子どもたちであったという。De Bellis & Putnumは、虐待（Maltreatment）という慢性のストレッサーが引き起こした免疫力の低下であろうと再検討している[7]。さらにこうしたストレスが脳の発達に対してなにかしら有害な影響を与える可能性を示唆した。

虐待（Maltreatment）と神経伝達物質の検討

表2　虐待を受けた子どもたちに見られる症状

| 身体面 | 行動面 | 精神・神経面 |
|---|---|---|
| 1）低身長・低体重・成長障害 | 1）過食・盗食・異食・食欲不振 | 1）運動発達の遅れ |
| 2）皮膚外傷 | 2）便尿失禁 | 2）情緒発達の遅れ |
| 3）骨折・脱臼・骨端破壊 | 3）常同運動 | 3）言語発達の遅れ |
| 4）火傷 | 4）自傷行為 | 4）抑うつ |
| 5）頭部外傷 | 5）緘黙 | 5）不眠 |
| 6）内臓損傷 | 6）虚言 | 6）過敏 |
| 7）脊椎損傷・麻痺 | 7）盗み・万引き | 7）体が硬い |
| 8）網膜剥離などの眼症状 | 8）家出徘徊 | 8）無表情 |
| 9）栄養障害・飢餓 | 9）いやがらせ | 9）無気力 |
| 10）けいれん・てんかん | 10）集団不適応 | 10）頑固 |
| 11）下痢・嘔吐・消化不良 | 11）火遊び・放火 | 11）気分易変 |
| 12）循環障害 | 12）だらしなさ | 12）おちつきがない |
| 13）凍傷 | 13）いじめ | 13）人との距離がない |
| 14）歯牙脱落・舌損傷 | 14）器物破損・暴力 | 14）大人の顔色をうかがう |
| | 15）性的逸脱行動 | 15）転換・解離現象 |
| | 16）自殺企図 | 16）パニック |
| | | 17）心因性疼痛 |
| | | 18）チック |
| | | 19）不定愁訴 |
| | | 20）希死念慮 |

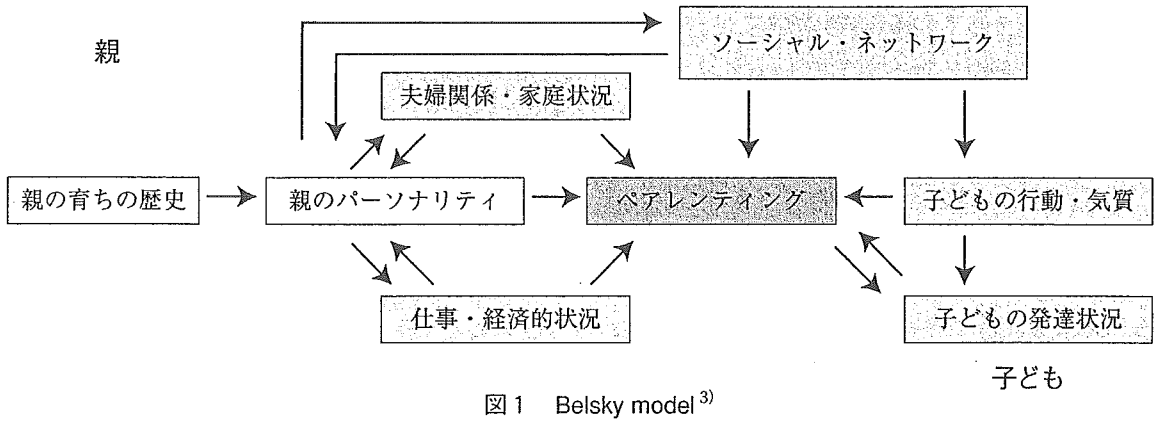


図1　Belsky model[3]

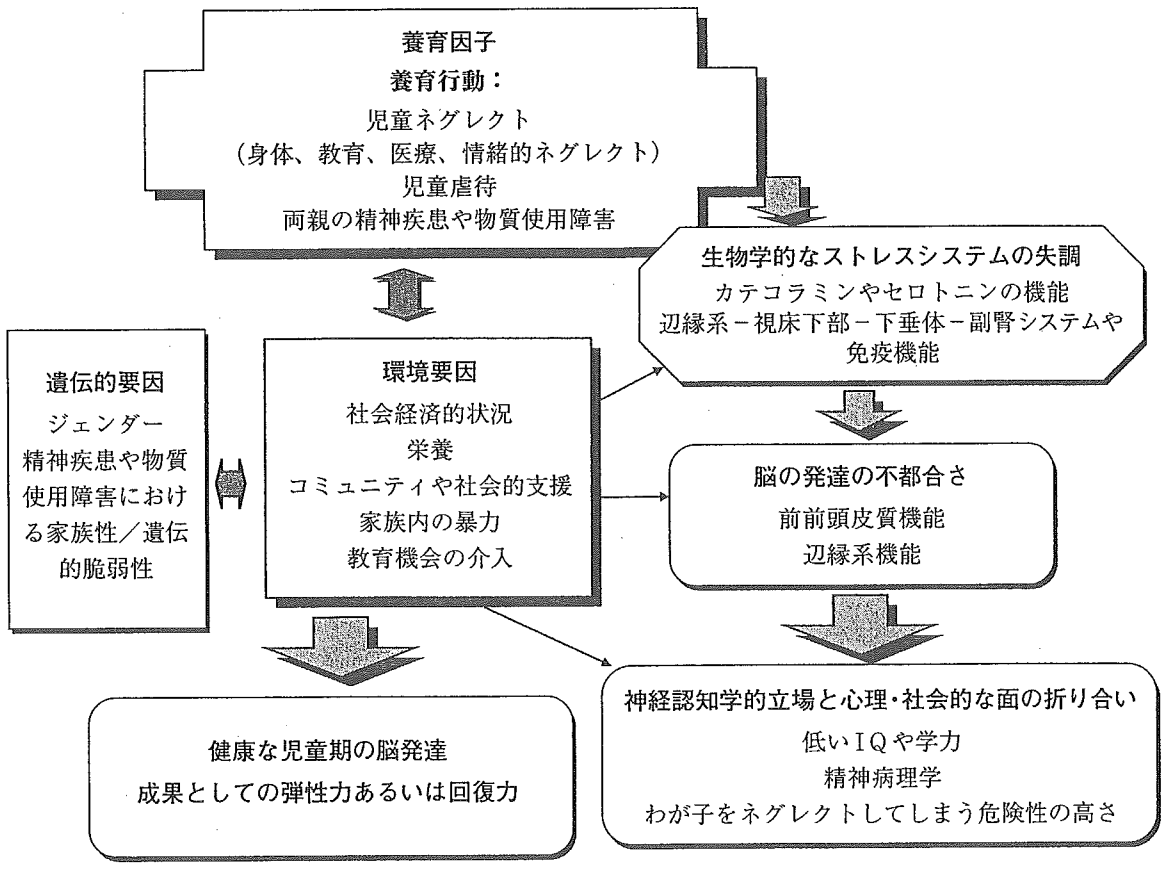


図２　A Developmental Traumatology for the Psychobiology of Neglect[15)]

では、セロトニンやドーパミンに変化が認められているという。セロトニンニューロンは、視床下部の攻撃動因系を抑制するだけでなく、大脳皮質にある攻撃抑制系の機能促進に関与するといわれている。ストレスにさらされた動物の研究では、扁桃体、前頭前頭野などのセロトニンレベルが減少を示したという。一方でドーパミンは前頭前頭野にまで影響を及ぼし、注意欠陥／多動性障害のある子どもたち同様に、不注意、過覚醒、新規場面への集中困難などを示し、時に妄想状態を引き起こす可能性も示唆された。

さらにAppelbaumら[1)]は、虐待（Maltreatment）を受けた子どもたちの発達には、認知面、運動面に遅れがあり、デンバー発達検査法では、４つの観察項目のうち３つ（個人－社会、微細運動－適応、言語）に遅れを認めた。

今後は、免疫機能との関連に加え、認知発達面、画像診断面での解明が急がれる。

歴史的な見解から先端的な研究を概括すると、虐待（Maltreatment）が子どもの発達、特に脳の発達になにかしら負の影響を及ぼしている可能性は否定できないと思われる[8)]。しかし、大切なことは、これらが不当に強調されすぎてしまわないように監視することであろう。

## 発達障害が養育状況に与える影響

発達障害とは、発達時期に多くの要因が絡み合い、その人にあるべき本来の機能に障害が与えられたものと理解される。本質的な特徴は、主要な障害が認知・言語・運動あるいは社会的技能の獲得におけるアンバランスさの存在ということになる。

発達障害学の進歩は、高い医療介護度を必要と

する重症心身障害から軽度の機能障害までへと、両極に広いすそ野を作り出している。本論では、高機能広汎性発達障害、注意欠陥／多動性障害、学習障害、発達性協調運動障害、軽度知的障害などの、いわゆる「軽度発達障害」を主に想定している[25]（図3）。大きな理由は、軽度発達障害のある子どもたちと親との出会いに比べて、機能的に重度の障害といわれる重度発達障害のある子どもたちとの接触が極めて少なかった、という私の個人的事情からである。そのため幾分偏った経験からの見解になることを断っておきたい。

この軽度発達障害グループは、発達のアンバランスさの特性は個々に異なるも、なんらかの発達のつまずきがあるとは思われにくく、わざとしているとか、親のしつけがなっていないといった誤解にさらされやすく、正しい診断を求めて医療や相談機関を訪れても、時には判断や診断が明確になりにくいという、発達のアンバランスさの確認が難しいという特性をもっている。さらに、子どもたちの年齢や保育・教育的支援といった環境の

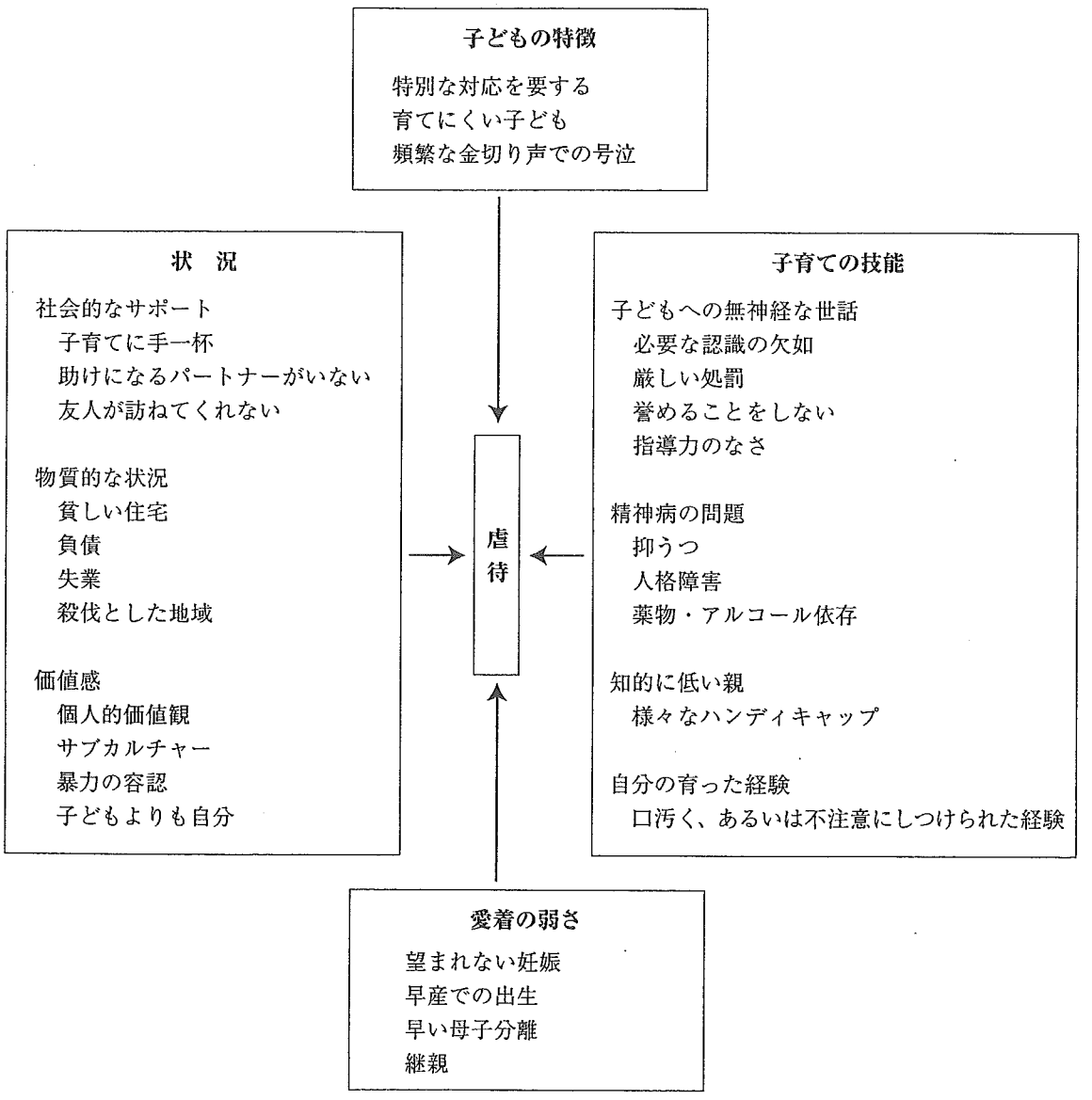


図3　児童虐待が生まれる要因
Robert Goodman, Stephen Scott: Maltreatment of Children. In Child Psychiatry, 1997.

影響を受けやすく、ここでも当人や養育者が責められるという誤解が生じやすい[25]。

正しく理解される機会が少なく、一方的に責められることから、当人や養育者は傷つき、周囲への不信感や、自己評価の低下といった二次的な問題を抱えてしまうことになりやすい。

軽度発達障害は、発達面からは軽いアンバランスさでもあるが、日常生活を送る上では、大きな生きにくさを抱えてしまいやすいという特徴をもっている。

私は、臨床の現場で軽度発達障害のある子どもにどう向き合ったらよいのだろうかと、途方に暮れ、不安でいっぱいの養育者とよく出会う。なかには「この子が小さい頃は、私は鬼のように叱っていました」、「きっと今なら虐待といわれるような関わりをしてきたように思います」、「わかっているのです。この子がそれが出来ないということがわかっていても、どうしてもイライラして叩いてしまうのです」といった話を聞くこともある。

「子育てが辛く思える、子どもがかわいく思えない」と答えた母親が8割以上を超える、という育児雑誌の調査結果[20]から示される元来の子育ての困難性に加え、なかなか理解しがたい「軽度発達障害」の特性は、親子間に「不適切な関係」を生じやすくする可能性があるのかもしれない。

一方で、Cowenら[6]は、保健師による初期介入の必要な母子、特に虐待（Maltreatment）が疑われるあるいはハイリスクな家族のタイプを以下の4つに分けている。

1）環境的に不利な子ども（社会経済的危機、独り親、思春期の母、不適切な支援を受けストレスにさらされている親）
2）生物学的に不利な子ども（低体重児、極小未熟児、急性、慢性疾患のために新生児集中治療室を利用する子ども）
3）発達の遅れ、偏り、障害のある子ども
4）環境と生物学的両面に危機をもつ子ども

育児に困難さを感じる養育者、家族が、発達障害のある子どもの養育者だけではないことは、あまりにも自明である。

そもそも、虐待を生み出すリスク要因については、これまで親側[21]、子ども側[27]からの精神医学的検討や、家庭・地域などを視野にいれた社会学的モデル[3,4]など、様々な視点で検討されてきた（図3）。しかし同じようなリスク因子をもっていても、虐待が発生する時としない場合がある。その違いはなんであろう。少なくともリスク因子＝虐待の発生と規定することはできない[22]。

この問題への仮説的な回答として、発達生態学的モデル[4]を援用した虐待発生モデルに、暴力のサイクル論[29]と段階的発生理論を統合したモデル[30]を提案した[26]（図4）。

このモデルは、子どもを取り巻く環境としてのミクロシステム（家族）、エクソシステム（地域）、マクロシステム（社会・文化）という発達生態学的理論を援用し、リスク因子と補償因子の存在を想定している。さらに各システムに生じるリスク因子と補償因子には、それぞれに永続的なものと、一時的なものがあり、一時的なものは永続的なものを強化・増強する役割をもつ。これらは日常生活上で常にバランスよく維持されているとは限らない。特に子どもと大人の関係は、育てられる者であった大人が、育てる者へと、コペルニクス的転回をするとき[14]でもある。育てる者になるためには、大人自身が「ほどほどに良く育てられた」歴史を持っていることが大切である。育てる者になるときに、その歴史がフラッシュバックするという。

養育者が育てられたように育てるとき、子どもが育てられたように育つと安定した関係が成立する。思うように育たないことは、自己否定に近い経験となる。軽度発達障害の有無が負担になるとしたら、このときかもしれない。軽度発達障害の特徴と生じやすい誤解について、簡単に示す（表3）。

発達障害のある子どもとない子どもにおける虐待遭遇率は、細川ら[10]の報告では、ネグレクトを受けている割合が高く、知的障害のある子どもに多いと言われている。Sullivanら[24]の調査によると、障害（知的障害、身体障害、学習障害、広

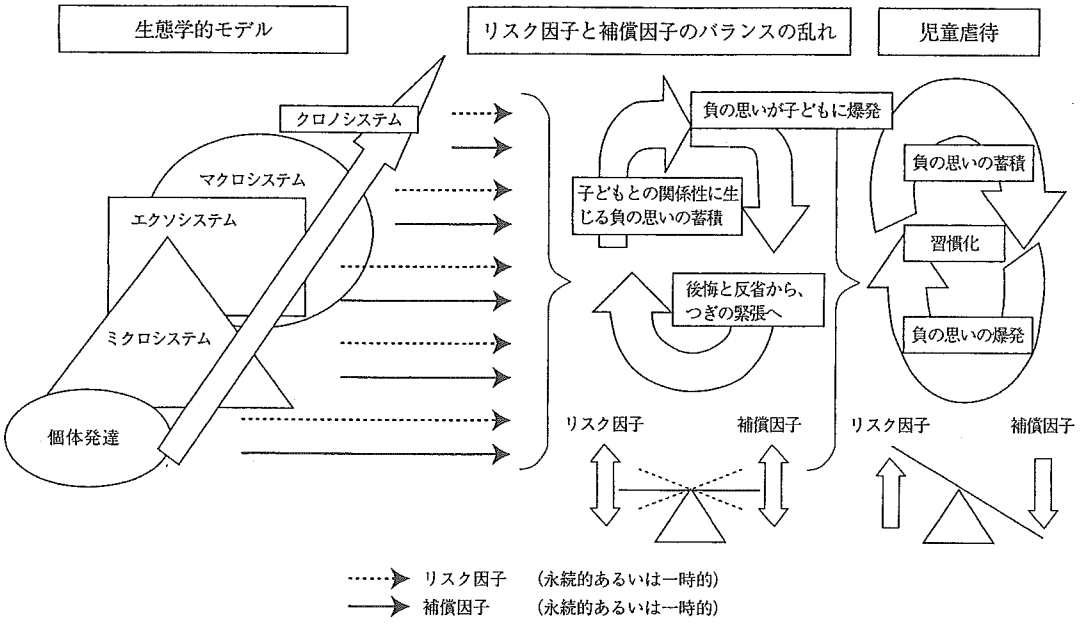


図4　生態学的見地に立つ児童虐待の発生・慢性化モデル

表3　軽度発達障害の特徴と生じやすい誤解

| 軽度発達障害 | 特徴 | 誤解 |
|---|---|---|
| 広汎性発達障害<br>（自閉症、アスペルガー症候群などの総称）<br>自閉症スペクトラムとも呼ばれる<br>IQが70以上を高機能という | 1）関わり合いの拒否（社会性の障害）<br>2）言葉・雰囲気のやりとりがうまくいかない（コミュニケーションの障害）<br>3）本来の遊びかたができない、こだわり（想像力の障害）、同じ行動の繰り返し（行動の障害） | ＜保護者への批判＞<br>人との関わりが取れないのは、愛情をもって育てられていないから<br>言葉かけや関わりが希薄、大切にされていない<br>＜子どもへの批判＞<br>わがまま、自分勝手 |
| 注意欠陥／多動性障害<br>（ADHD） | 1）多動<br>2）注意散漫・不注意<br>3）衝動性 | ＜保護者への批判＞<br>社会的ルールなどきちんとしつけていない<br>＜子どもへの批判＞<br>わがまま、自分勝手 |
| 学習障害<br>（LD） | 読み、書字、算数（計算）などの学習能力が、年齢、知能レベル、受けている教育により、期待できる程度よりも低い状態 | ＜保護者への批判＞<br>日頃の学習指導をしていない<br>＜子どもへの批判＞<br>やる気がない |
| 発達性協調運動障害 | 協調運動の発達が、年齢、知能レベルに比べ劣る、粗大運動の遅れ、不器用 | ＜保護者への批判＞<br>手をかけていない<br>＜子どもへの批判＞<br>やる気がない |

汎性発達障害）のある子どもへの虐待は、障害のない子どもの3.4倍という。

## おわりに

虐待（Maltreatment）が子どもの発達、特に脳の発達になにかしら負の影響を及ぼしている可能性は否定できないが、その逆を明らかにすることはできない。虐待（Maltreatment）が生まれるときは、相互関係のつまずきと、それぞれの資質と、運とタイミングの絡み合いと、その悪循環を阻止できない状況を想定するしかない。

くれぐれも短絡的に結論を急がないことである。しかし、子どもと養育者が支援されるために最終的に必要なフィールドとは、一般の日常生活場面である。

虐待問題を防ぐ方向性を国家的に導き出せないこと、導き出すために真剣に対策を練らないことは、国家的虐待であると、最後に主張しておきたい。

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