https://doi.org/10.5607/en.2020.29.1.11
Exp Neurobiol. 2020 Feb;29(1):11-26.
pISSN 1226-2560 • eISSN 2093-8144

Original Article

Experimental Neurobiology

Distribution of Cadherin in the Parahippocampal Area of Developing Domestic Chicken Embryos

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Hippocampal formation is important in spatial learning and memory. Members of the cadherin superfamily are observed in the neural system with diverse spatial and temporal expression patterns and are involved in many biological processes. To date, the avian hippocampal formation is not well understood. In this study, we examined the expression of cadherin mRNA in chicken and mouse brains to investigate the morphological and cytoarchitectural bases of hippocampal formation. Profiles of the spatiotemporal expression of cadherin mRNAs in the developing chicken embryonic parahippocampal area (APH) are provided, and layer-specific expression and spatiotemporal expression were observed in different subdivisions of the APH. That fact that some cadherins (Cdh2, Cdh8, Pcdh8 and Pcdh10) showed conserved regional expression both in the hippocampus and entorhinal cortex of mice and the hippocampal formation of chickens partially confirmed the structural homology proposed by previous scientists. This study indicates that some cadherins can be used as special markers of the avian hippocampal formation.

Key words: Hippocampus, Parahippocampal area, Cadherin, Chicken embryos, Avian

INTRODUCTION

Hippocampal formation is important in spatial learning and memory [1]. However, the molecular and cytoarchitecture bases are still not clear in evolution, and the homology between avian and mammalian species needs to be clarified [2, 3].

Avian hippocampal formation includes the hippocampus and the parahippocampal area (APH). This formation occurs in the medial and dorsomedial pallium and extends laterally to part of the caudolateral pallium. The avian APH does not have clear boundaries with the hippocampus. Hippocampal formation was divided into the hippocampus and APH first [2, 4]. Later, hippocampal formation was divided into seven subdivisions in other studies based on the different immunoactivities of neural peptides antibodies [5, 6]. Some researchers subsequently divided hippocampal formation into five subdivisions: dorsomedial (DM) [7], dorsolateral (DL), ventral core, ventrolateral area of the V-shaped layer and ventromedial area of the V-shaped layer [8, 9]. Recently, the APH has been considered to correspond to the DM and DL subdivisions (Fig. 1A) [10]. The APH has also been divided into four portions, the medial APH (APHm), the intermediate APH (APHi), the lateral APH (APHl) and the caudolateral APH (APHcl), in chicken embryos (Fig. 1B) [11]. A small portion of the superficial corticoid dorsolateral area is also included in the caudolateral APH part [12]. The APH is a structure that develops at a later stage during the embryonic period in avian species. This long and thin

Received September 27, 2019, Revised January 24, 2020,
Accepted January 24, 2020

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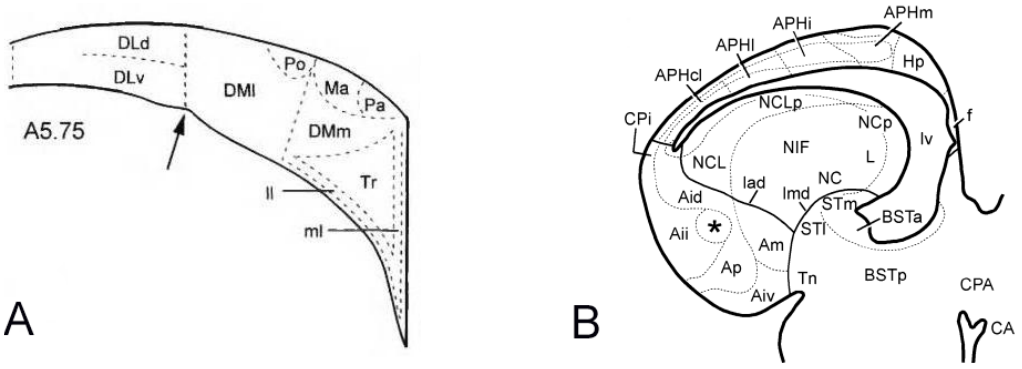

Fig. 1. Schematic illustration of subdivisions respectively in the pigeon hippocampal formation (A) and chicken embryo brain (B) [2, 11].

cortical structure is defined as overlaid on the dorsal part of the lateral ventricle. The APH is a special cortical region associated with learning, memory and other cognitive processes [13]. The avian hippocampal formation region is functionally homologous to the hippocampal region in mammals [14, 15], and even their cytoarchitecture and morphology are different. The hippocampal region in mammals includes the subiculum, CA1-3 and dentate gyrus. Based on the intrinsic neuronal circuits, the avian V-shaped layer has been suggested to be homologous with the dentate gyrus in mammals. Tract tracing and kainic acid lesions provide support indicating that the dorsomedial subdivision has similar morphological properties to those of mammalian Ammon's horn and the subiculum [2, 10]. The dorsolateral subdivision might be similar to the mammalian entorhinal cortex according to inputs projected to the APH from the olfactory bulb and visual system in pigeons [16-19].

During chicken embryo development, cadherins were identified as single-transmembrane glycoproteins that mainly contribute to cell–cell adhesion [20, 21]. Cadherins are important during developmental morphogenesis and differentiation, for the maintenance of cell environment homeostasis and for the integrity of tissue. Cadherin expression is under the control of gene transcription, translation and protein trafficking, which regulate the biological activity of cadherin during development [21]. Changes in cadherin expression play a necessary role in cell sorting and tissue growth, and during development, the expression of cadherin shows a spatiotemporally regulated order [22, 23]. Cadherin superfamily can be divided into different subfamilies such as classic cadherins, protocadherins, desmosomal cadherins and Flamingo cadherins. Different cadherin molecules are expressed in distinct cell types and regions in the embryonic central nervous system (CNS) [22]. Depending on its different adhesive ability, cadherin takes part in cell sorting and is beneficial for cell adhesion in different tissues. In the CNS, cadherins regulate synapse formation, synaptic plasticity, and dendrite growth [23]. Some protocadherin molecules are considered related to neuronal circuitry formation and initiate different connections within the developing CNS [24]. Different functions may emerge in development due to the various members of the cadherin family [23, 25]. The chicken embryo is widely used as an experimental model of development, differentiation and morphology. The embryonic chicken brain is a useful model for investigating prenatal development and gene function in the avian CNS [26]. In this study, the intermediate development stage, E14, and the late development stage, E18, were employed. Observation of the distribution of cadherin mRNA was carried out in the developing chicken APH to study APH development. We tried to define different APH subdivisions using various cadherin molecules as markers and to provide a potential molecular basis for differentiating structural connections in the APH development.

MATERIALS AND METHODS

Materials

Fertilized eggs from White Leghorn chickens (Gallus gallus domesticus) were purchased from a local farm and incubated at 38℃ and 60% humidity in a humidified incubator. Embryos were staged according to Hamburger and Hamilton stages (HH) [25]. Three-month-old wild-type mice were employed in this study, and they were kindly provided by Dr. Christoph Kaether (Leibnitz Institute of Age Research-Fritz Lipmann Institute, Germany). All mice were kept under standard animal care conditions and were fed ad libitum. Each group had 3~4 animal samples.

The minimum number of animals was used, and animal suffering was minimized in this study using national and institutional guidelines. Digoxigenin-labeled antisense and sense cRNA probes of cadherin and protocadherin molecules were synthesized *in vitro* using previously described specific plasmids according to the manufacturer's instructions (Roche, Mannheim, Germany) [27-30]. The GenBank accession numbers are listed in Table 1.

 https://doi.org/10.5607/en.2020.29.1.11

Table 1. Information of different chicken and mouse cadherins

Cadherin	Genbank number	Cadherin	Genbank number
Chicken Cdh2	NM_001001615	Mouse Cdh2	NM_007664.5
Chicken Cdh4	NM_001004391	Mouse Cdh4	NM_001316723.1
Chicken Cdh6B	NM_001001758	Mouse Cdh6	NM_007666.4
Chicken Cdh7	NM_204187	Mouse Cdh7	NM_001316743.1
Chicken Cdh8	NM_001100289	Mouse Cdh8	NM_001039154.2
Chicken Cdh9	XM_001231540.5	Mouse Cdh11	NM_009866.5
Chicken Cdh11	NM_001004371	Mouse Pcdh1	NM_029357.3
Chicken Cdh12	XM_418999.4	Mouse Pcdh7	NM_001122758.2
Chicken Cdh18	XM_426046.6	Mouse Pcdh8	NM_001042726.3
Chicken Cdh19	NM_001100287.1	Mouse Pcdh9	NM_001081377.3
Chicken Cdh20	NM_204134.1	Mouse Pcdh10	NM_001098170.1
Chicken Pcdh1	NM_001045827	Mouse Pcdh17	NM_001013753.2
Chicken Pcdh7	XM_015285689	Mouse Pcdh19	NM_001105245.1
Chicken Pcdh8	NM_001098609		
Chicken Pcdh9	XM_416995		
Chicken Pcdh10	NM_214672		
Chicken Pcdh15	NM_001044654.1		
Chicken Pcdh17	XM_015276818		
Chicken Pcdh18	XM_004940935.3		
Chicken Pcdh19	NM_001098607		
Chicken Pcdh21	NM_001001759.1		

Tissue preparation and Cyrostat sectioning

When the embryos were at the desired stages, eggs were deeply anesthetized by chilling on ice. After sterilizing the shells with 75% alcohol, brains from the embryos were harvested and fixed in 4% paraformaldehyde (PFA) at 4℃ for 4 hours. The fixed brains were subsequently dehydrated in 15% and 30% sucrose in Hanks' balanced salt solution (HBSS). Dehydrated brains were embedded with Tissue-Tek O.C.T. Compound (Sakura Finetek Europe, Netherlands) and stored at -80℃ until cryostat sectioning. Wild-type mice were decapitated after anaesthesia and dissected on ice. The brains from adult mice were removed rapidly and frozen in -40℃ 2-methylbutane and then stored at -80℃ until cryostat sectioning.

The brains were cut into 20 μm thick coronal sections, and the frozen sections were immediately collected onto microscope slides. One adjacent slide from each series was stained by thionin for identifying the basic neuronal structures.

In situ hybridization

In situ hybridization was carried out using a previously described procedure [29]. Cryostat sections were fixed in 4% paraformaldehyde, washed with phosphate-buffered saline (PBS), and treated with 1 μg/ml proteinase K (Sigma-Aldrich, San Francisco, California, the United States) and 0.25% acetic anhydride. Sections were hybridized overnight with chicken and mouse cadherin cRNA probes (approximately 300 ng/slide) at 70℃. Then, the sections were washed in 5×saline sodium citrate buffer (SSC) and 2×SSC at 60℃, and after RNase A (20 μg/ml, Sigma-Aldrich) treatment, the slides were sequentially rinsed with 2×SSC and 0.1×SSC at room temperature. Alkaline phosphatase-coupled anti-digoxigenin Fab fragments (anti-Dig-Fab AP, Roche Diagnostics) were applied overnight at 4℃ after washing. For visualization of the target mRNAs, sections were incubated with a substrate solution that contained 0.03% nitrobluetetrazolium (NBT) and 0.02% 5-bromo-4-chloro-3-indolyl-phosphate (BCIP) for 1~3 days at room temperature or 4℃. Finally, the sections were dehydrated by a concentration gradient of alcohol, equilibrated with xylene and then mounted with Entellan (Merck Millipore).

Image Analysis

All sections were observed under a transmission light microscope (BX40, Olympus). Images were acquired by an Olympus DP70 digital camera and a confocal laser scanning microscope (SP5, Leica Microsystems). Essential adjustments of contrast and brightness in photographs were carried out with Photoshop software (Adobe).

RESULTS

Expression of cadherin in the APH

Cadherin mRNAs showed spatial and temporal expression patterns in the developing chifcken APH (Fig. 2~4). *In situ* hybridization signals of Cdh18, Cdh19, Pcdh18, and Pcdh21 were almost

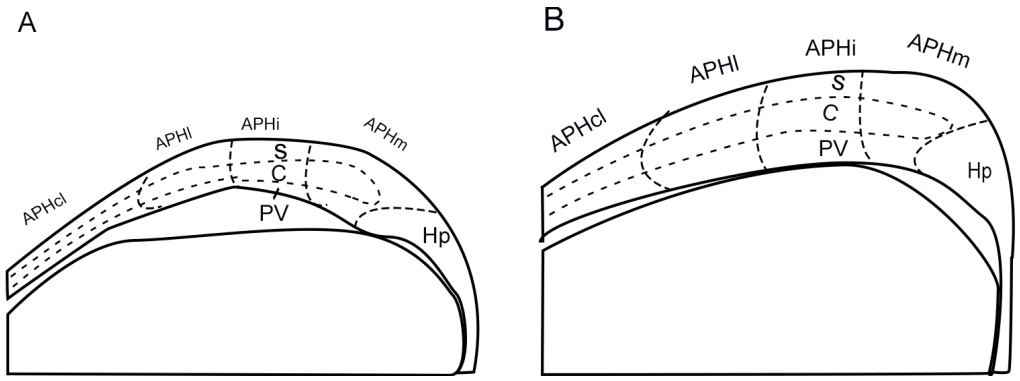

Fig. 2. Schematic illustration of E14 and E18 chicken embryo brain. (A) Embryos at intermediate development stage E14. (B) Embryos at late development stage E18. HP, hippocampus; APHm, the medial part of APH; APHi, the intermedial part of APH; APHl, the lateral part of APH; APHcl, the caudolateral part of APH; S, the superficial layer; C, the cortical plate; PV, the periventricular layer. Dashed lines indicate the division between subregions and layers.

negative in the APH (Fig. 3S~3V and 4Q, 4R, 4U, 4V). The expression details of common cadherin molecules in chickens could also be found in mice were examined under magnification and are listed in Table 2~5 (Fig. 5~8). Subregions (APHm, APHi, APHl, and APHcl) and layers (the superficial layer, the cortical plate, and the periventricular layer) of the APH were analysed using definitions proposed by Redies et al. [11, 12].

Expression of cadherins in the developing chicken APHm

Layer-specific expression was observed in Cdh4, Cdh6B, Cdh7, Cdh9, Cdh11, Cdh18, Cdh20, Pcdh1, Pcdh8, Pcdh9, and Pcdh15 in the APHm at E14 and E18 (Table 2, Fig. 3E~3J, 3M~3P, 3S, 3T, 3W, 3X and Fig. 4C, 4D, 4G~4J, 4M, 4N). Expression of Cdh2 was strong in all three layers of the APHm at E14, and the hybridization signal became weak at E18 (Fig. 5A and 5B). Cdh4 mRNA showed weak expression in the superficial and cortical layers of the APHm both at E14 and E18. The hybridization signal of Cdh4 was nearly negative in the periventricular layer (Fig. 5C and 5D). Cdh6B mRNA showed a weak to moderate signal in the superficial layers at E14 and E18. The hybridization signal of Cdh6B was weak in the lower part of the APHm (Fig. 5E and 5F). Cdh7 mRNA could be detected in the superficial layer of the APHm, while the signal was weak in the cortical and periventricular layers at E14. At E18, the hybridization signal of Cdh7 was weak in all three layers of the APHm (Fig. 5G and 5H). Cdh8 mRNA expression was very weak in the lower part of the APHm both at E14 and E18 (Fig. 5I and 5J). Strong signals of Cdh11 mRNA were detected in the cortical and periventricular layers of the APHm at E14 and E18. Relatively weaker Cdh11 mRNA expression was observed in the superficial layer (Fig. 5K and 5L).

Pcdh1 mRNA was expressed strongly in the cortical and periventricular layers of the APHm at E14 and in all three layers at E18 (Fig. 5M and 5N). The Pcdh7 mRNA signal was negative in the APHm at E14 but was expressed in the APHm at E18 (Fig. 5O and 5P). Pcdh8 mRNA-positive cells could be observed in the periventricular layer of the APHm at E14 and E18 (Fig. 5Q and 5R). A moderate Pcdh9 mRNA signal was detected in the superficial and cortical layers of the APHm at E14 and E18 (Fig. 5S and 5T). Pcdh10 mRNA showed a stronger signal in the lateral part of the APHm than that in the medial part (Fig. 5U and 5V). Pcdh17 mRNA was expressed strongly in all three layers of the APHm at E14, but the strength of the signal was moderate in the cortical and periventricular layers at E18 (Fig. 5W and 5X). Pcdh19 mRNA showed strong expression in all three layers of the APHm at E14 and moderate expression at E18 (Fig. 5Y and 5Z).

Expression of cadherins in the developing chicken APHi

In the APHi, layer-specific expression could be observed in the *in situ* hybridization results of Cdh4, Cdh6B, Cdh7, Cdh8, Cdh9, Cdh11, Cdh12, Cdh20, Pcdh9 and Pcdh19 at E14 and E18 (Table 3, Fig. 3E~3R, 3W, 3X and Fig. 4I, 4J, 4S, 4T).

Cdh2 mRNA was detected in all three layers of the APHi at E14 and E18. The hybridization signal of Cdh2 in APHi was strong at E14 and moderate at E18 (Fig. 6A and 6B). Cdh4 mRNA showed moderate expression in the cortical layer of the APHi both at E14 and E18 (Fig. 6C and 6D). Cdh6B mRNA showed a moderate signal in the periventricular layer of the APHi at E14 and E18 (Fig. 6E and 6F). Cdh7 mRNA was detected in the superficial and cortical layers of the APHi, whereas the signal was weak in the periventricular layers at E14 (Fig. 6G). At E18, the hybridization signal of Cdh7 could be observed in all three layers of the APHi (Fig. 6H). Cdh8 mRNA expression was weak in the APHi (Fig. 6I and 6J).

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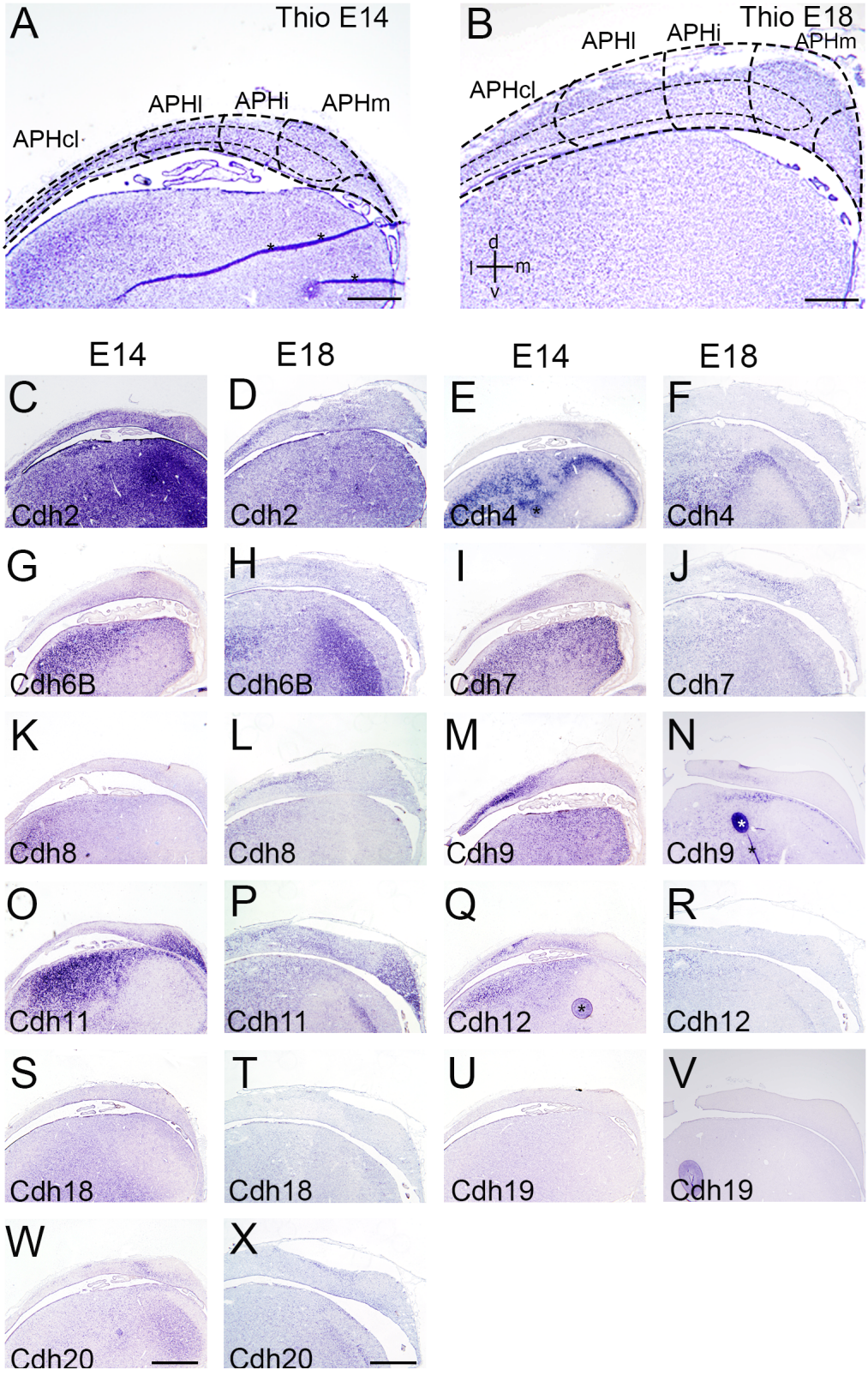

Fig. 3. Overview of classic cadherin mRNA expression in the APH of developing chicken embryos at E14 and E18. (A, B) Thionin staining for anatomical structures. (C, D) Cdh2. (E, F) Cdh4. (G, H) Cdh6B. (I, J) Cdh7. (K, L) Cdh8. (M, N) Cdh9. (O, P) Cdh11. (Q, R) Cdh12. (S, T) Cdh18. (U, V) Cdh19. (W, X) Cdh20. APHm, the medial part of the APH; APHi, the intermedial part of the APH; APHl, the lateral part of the APH; APHcl, the caudolateral part of the APH. Dashed lines indicate the division between subregions. The asterisks indicate artefacts. Scale bar=1 mm.

A moderate signal of Cdh11 mRNA was detected in the periventricular layer of the APHi (Fig. 6K and 6L).

Pcdh1 mRNA expression was strong in all three layers of the APHi at E14 and E18 (Fig. 6M and 6N). Pcdh7 mRNA expression was weak in the cortical layer of the APHi (Fig. 6O and 6P). Pcdh8 mRNA was expressed weakly in the APHi at E14, and the

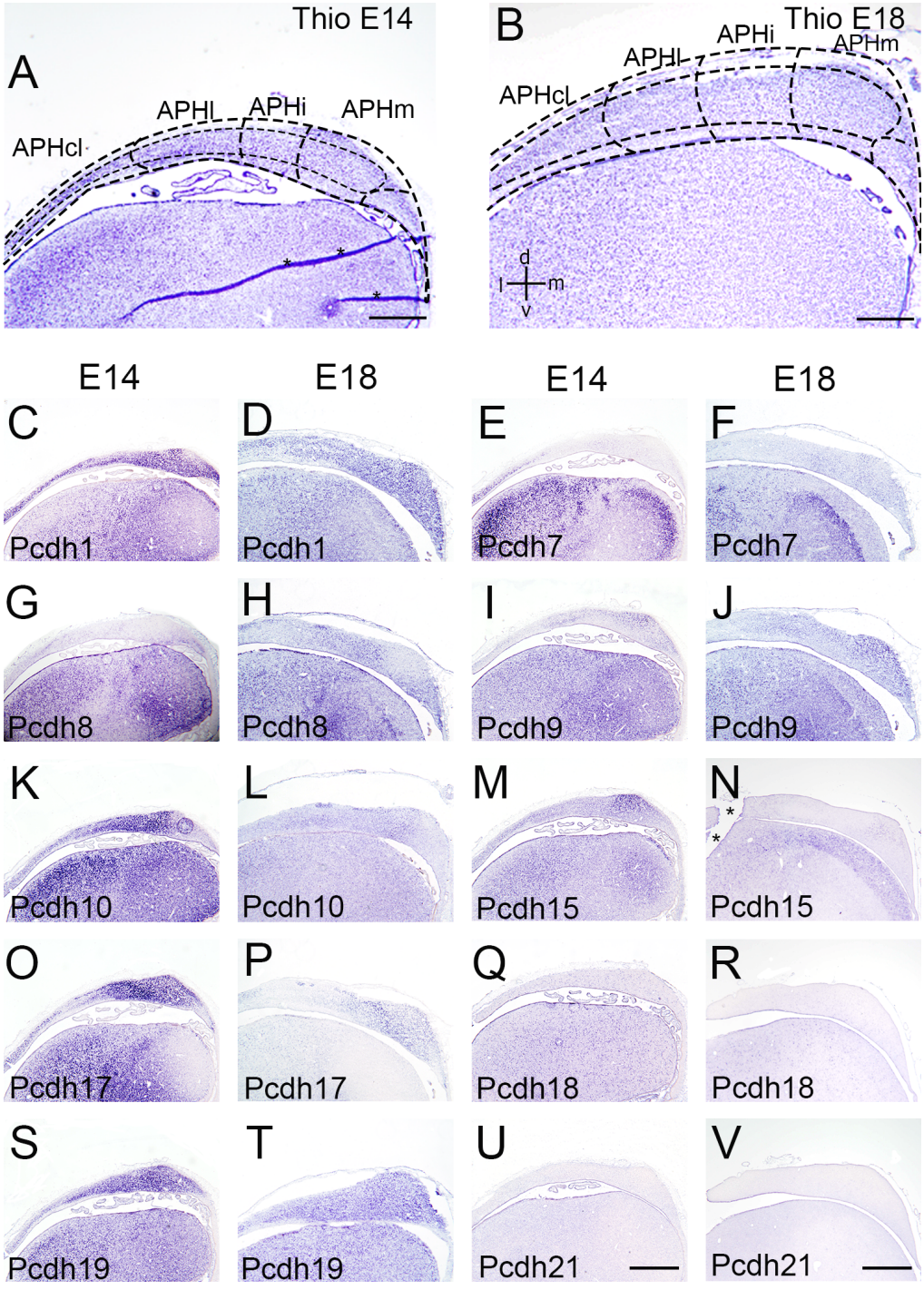

Fig. 4. Overview of protocadherin cadherin mRNA expression in the APH of developing chicken embryos at E14 and E18. (A, B) Thionin staining for anatomical structures. (C, D) Pcdh1. (E, F) Pcdh7. (G, H) Pcdh8. (I, J) Pcdh9. (K, L) Pcdh10. (M, N) Pcdh15. (O, P) Pcdh17. (Q, R) Pcdh18. (S, T) Pcdh19. (U, V) Pcdh21. APHm, the medial part of the APH; APHi, the intermedial part of the APH; APHl, the lateral part of the APH; APHcl, the caudolateral part of the APH. Dashed lines indicate the division between subregions. The asterisks indicate artefacts. Scale bar=1 mm.

expression was moderate in the APHi at E18 (Fig. 6Q and 6R). A moderate Pcdh9 mRNA signal was detected in the upper layers of the APHi both at E14 and E18 (Fig. 6S and 6T). A strong signal of Pcdh10 mRNA was observed in all three layers of the APHi at E14, and a weak to moderate signal was detected at E18 (Fig. 6U and 6V). Pcdh17 mRNA was expressed strongly in all three layers of the APHi at E14, but the signal was moderate at E18 (Fig. 6W and 6X). Pcdh19 mRNA showed strong expression in all three layers of the APHi at E14 and moderate expression at E18 (Fig. 6Y and 6Z).

Expression of cadherins in the developing chicken APHl

Layer-specific expression in the APHl was shown by *in situ* hybridization positive signals of Cdh6B, Cdh7, Cdh8, Cdh9, Cdh11, Cdh12, Cdh20, Pcdh1, Pcdh8, Pcdh9, Pcdh10, Pcdh15, Pcdh17,

https://doi.org/10.5607/en.2020.29.1.11

Table 2. Expression level of 13 Cadherins in APHm of the developing chicken embryo*

Name	superficial layer	E14 cortical plate	periventricular layer	superficial layer	E18 cortical plate	periventricular layer
Cdh2	+++	+++	+++	+	+	+
Cdh4	+	+	-	+	+	-
Cdh6B	++	+	+	+	+	+
Cdh7	++	+	+	+	+	+
Cdh8	-	+	+	-	+	+
Cdh11	++	+++	+++	++	+++	+++
Pcdh1	++	+++	+++	+++	+++	+++
Pcdh7	-	-	-	+	+	+
Pcdh8	-	-	+	-	-	+
Pcdh9	++	++	+	++	++	+
Pcdh10	+++	+++	+++	++	++	++
Pcdh17	+++	+++	+++	+++	++	++
Pcdh19	+++	+++	+++	++	++	++

*Expression level: -, negative, no cell positive or less than 10% positive; +, weak, single cells (up about 20%) positive; ++, moderate, numerous cells (about 20~80%) positive; +++, strong, all or almost all cells (more than 80%) positive.

Table 3. Expression level of 13 Cadherins in APHi of the developing chicken embryo*

Name	superficial layer	E14 cortical plate	periventricular layer	superficial layer	E18 cortical plate	periventricular layer
Cdh2	+++	+++	+++	++	++	++
Cdh4	-	++	+	-	++	+
Cdh6B	+	+	++	+	+	++
Cdh7	++	++	+	++	++	++
Cdh8	+	+	+	+	+	+
Cdh11	+	+	++	+	+	++
Pcdh1	+++	+++	+++	+++	+++	+++
Pcdh7	-	+	-	-	+	+
Pcdh8	+	+	+	++	++	++
Pcdh9	++	++	+	++	++	+
Pcdh10	+++	+++	+++	+	++	++
Pcdh17	+++	+++	+++	++	++	++
Pcdh19	+++	+++	+++	++	++	++

*Expression level: -, negative, no cell positive or less than 10% positive; +, weak, single cells (up about 20%) positive; ++, moderate, numerous cells (about 20~80%) positive; +++, strong, all or almost all cells (more than 80%) positive.

Pcdh18, and Pcdh19 (Table 4, Fig. 3G~3R, 3W, 3X and Fig. 4C, 4D, 4G~4T).

Cdh2 mRNA was detected in all three layers of the APHl, and the signal was weaker in the upper part at E18 (Fig. 7A and 7B). The *in situ* hybridization signal of Cdh4 mRNA was weak in the APHl at E14 and E18 (Fig. 7C and 7D). Cdh6B mRNA showed a weak to moderate signal in the cortical plate and periventricular layer of the APHl at E14 (Fig. 7E). At E18, the expression of Cdh6B mRNA was shown in the cortical plate (Fig. 7F). The Cdh7 mRNA hybridization signal in the upper layer of the cortical plate was stronger compared with that in the lower layer of APHl at E14 and E18 (Fig. 7G and 7H). Cdh8 mRNA expression was weak in the cortical plate of the APHl at E14 (Fig. 7I). In E18, the Cdh8 mRNA showed a moderate signal (Fig. 7J). The hybridization signal of Cdh11 mRNA was detected in the superficial layer and cortical plate of the APHl at E14 and E18 (Fig. 7K and 7L). The expression of Cdh11 mRNA was weak in the upper part of the cortical plate and moderate in the lower part at E18 (Fig. 7L).

Pcdh1 mRNA expression was observed in the superficial layer and cortical plate of the APHl (Fig. 7M and 7N). The signal was moderate in three layers at E18. A weaker signal was shown in the middle sublayer of the cortical plate (Fig. 7N). Pcdh7 mRNA expression was almost negative in the APHl at E14 and E18 (Fig. 7O and 7P). Pcdh8 mRNA was expressed weakly in the cortical layer of the APHl at E14 (Fig. 7Q). At E18, scattered cells were observed in superficial and cortical layers of the APHl, and the signal gradually faded from a medial to lateral orientation (Fig. 7R). Moderate Pcdh9 mRNA expression was observed in the superficial layer and

Table 4. Expression level of 13 Cadherins in APHl of the developing chicken embryo*

Name	E14 superficial layer	E14 cortical plate	E14 periventricular layer	E18 superficial layer	E18 cortical plate	E18 periventricular layer
Cdh2	+++	+++	+++	++	++	++
Cdh4	-	+	-	-	+	-
Cdh6B	+	+	++	+	+	+
Cdh7	+	++	+	+	++	+
Cdh8	+	+	+	+	++	+
Cdh11	++	++	+	++	++	+
Pcdh1	+++	+++	+	++	++	+
Pcdh7	-	-	-	-	-	-
Pcdh8	+	+	+	+	+	+
Pcdh9	++	++	+	++	++	+
Pcdh10	+++	+++	++	++	+	+
Pcdh17	+++	+++	+	++	++	-
Pcdh19	+++	+++	+++	++	++	++

*Expression level: -, negative, no cell positive or less than 10% positive; +, weak, single cells (up about 20%) positive; ++, moderate, numerous cells (about 20~80%) positive; +++, strong, all or almost all cells (more than 80%) positive.

Table 5. Expression level of 13 Cadherins in APHcl of the developing chicken embryo*

Name	E14 superficial layer	E14 cortical plate	E14 periventricular layer	E18 superficial layer	E18 cortical plate	E18 periventricular layer
Cdh2	-	+++	-	-	++	-
Cdh4	-	-	-	-	-	-
Cdh6B	-	+	-	-	+	-
Cdh7	+	++	-	-	++	-
Cdh8	-	+	-	-	+	-
Cdh11	+	++	-	+	++	+
Pcdh1	+	++	-	++	++	-
Pcdh7	-	++	-	-	++	-
Pcdh8	-	+	-	+	+	-
Pcdh9	-	+	-	-	+	-
Pcdh10	+	++	-	+	+	-
Pcdh17	++	++	-	+	+	-
Pcdh19	++	++	-	+	+	-

*Expression level: -, negative, no cell positive or less than 10% positive; +, weak, single cells (up about 20%) positive; ++, moderate, numerous cells (about 20~80%) positive; +++, strong, all or almost all cells (more than 80%) positive.

cortical plate of the APHl. The Pcdh9 mRNA signal detected in the lower part of the cortical layer of the APHl was stronger than that in the upper part (Fig. 7S and 7T). A strong signal of Pcdh10 mRNA was observed in the superficial layer and cortical plate at E14, and a weaker signal was detected at E18. The upper part of the cortical plate only showed a negative to weak signal (Fig. 7U and 7V). Pcdh17 mRNA expressed strongly stained patches in the superficial layer of the APHl at E14, and the Pcdh17 mRNA expression faded gradually from a medial to lateral orientation in the cortical plate of the APHl. At E18, the signal was weaker than that at E14 (Fig. 7W and 7X). Pcdh19 mRNA showed strong expression in the cortical plate of the APHl at E14, and the *in situ* signal was moderate at E18 (Fig. 7Y and 7Z).

Expression of cadherins in the developing chicken APHcl

In the APHcl, layer-specific expression was observed in Cdh2, Cdh6B, Cdh7, Cdh8, Cdh9, Cdh11, Cdh12, Cdh20, Pcdh1, Pcdh7, Pcdh8, Pcdh9, Pcdh10, Pcdh15, Pcdh17 and Pcdh19 (Table 5, Fig. 3C, 3D, 3G~3R, 3W, 3X and Fig. 4C~4P, 4S, 4T).

Cdh2 mRNA was detected in the cortical plate of the APHcl at E14 and E18. The hybridization signal of Cdh2 in the APHcl was strong at E14 and became moderate at E18 (Fig. 8A and 8B). Cdh4 mRNA expressed a negative signal in the APHcl (Fig. 8C and 8D). Cdh6B, Cdh8, Pcdh8, and Pcdh9 mRNA showed a weak signal in the cortical plate of the APHcl at E14 and E18 (Fig. 8E, 8F, 8I, 8J, 8Q~8T). Cdh7 mRNA signal was detected in the cortical layers of the APHcl at E14 and E18. At E14, scattered cells with a positive signal were expressed medially in the upper part of the APHcl, and

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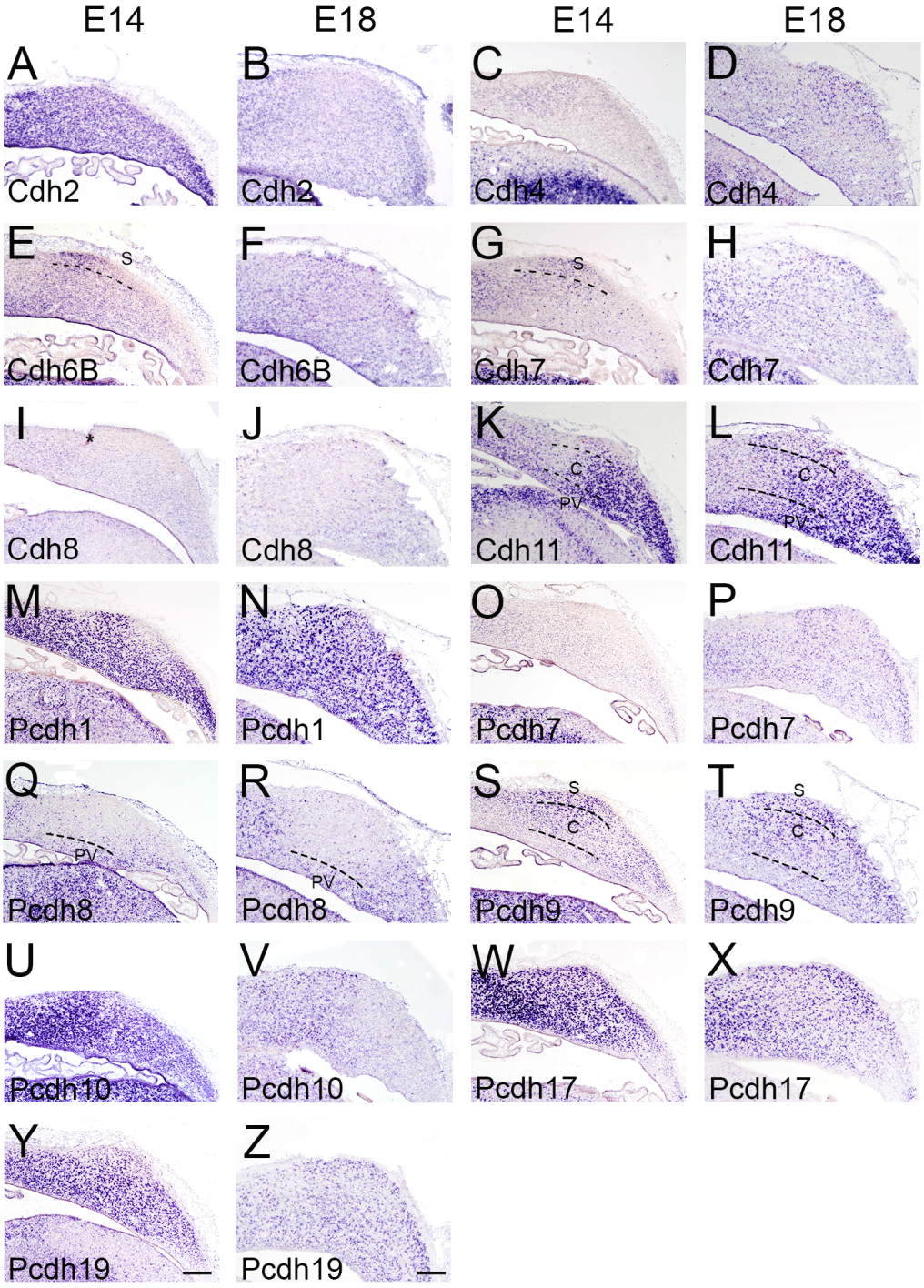

Fig. 5. Expression of cadherin mRNA in the APHm of developing chicken embryos at E14 and E18. (A, B) Cdh2. (C, D) Cdh4. (E, F) Cdh6B. (G, H) Cdh7. (I, J) Cdh8. (K, L) Cdh11. (M, N) Pcdh1. (O, P) Pcdh7. (Q, R) Pcdh8. (S, T) Pcdh9. (U, V) Pcdh10. (W, X) Pcdh17. (Y, Z) Pcdh19. S, the superficial layer; C, the cortical plate; PV, the periventricular layer. Dashed lines indicate the division between subregions and layers. The asterisks indicate artefacts. Scale bar=250 μm.

a moderate signal could be observed laterally in the cortical plate (Fig. 8G). At E18, Cdh7 mRNA showed a moderate signal in the cortical plate of the APHcl (Fig. 8H). A moderate *in situ* hybridization signal of Cdh11 and Pcdh7 mRNAs was detected in the cortical plate of the APHcl at E14 and E18 (Fig. 8K, 8L, 8O, and 8P). The expression of Pcdh1, Pcdh10, Pcdh17, and Pcdh19 were moderate in the cortical plate of the APHcl at E14 and became weaker at E18 (Fig. 8M, 8N, 8U~8Z).

Comparison of cadherin expression between chicken and mouse hippocampal formations

To investigate the possibility by using cadherins as markers to explore structural homology, we compared the expression of cadherin mRNAs in the hippocampal formation and parahippocampal areas of chicken and mice. Since the structure of the chicken telencephalon is relatively mature at 16 embryonic days, we chose the E18 chicken embryo and adult mouse brain sections

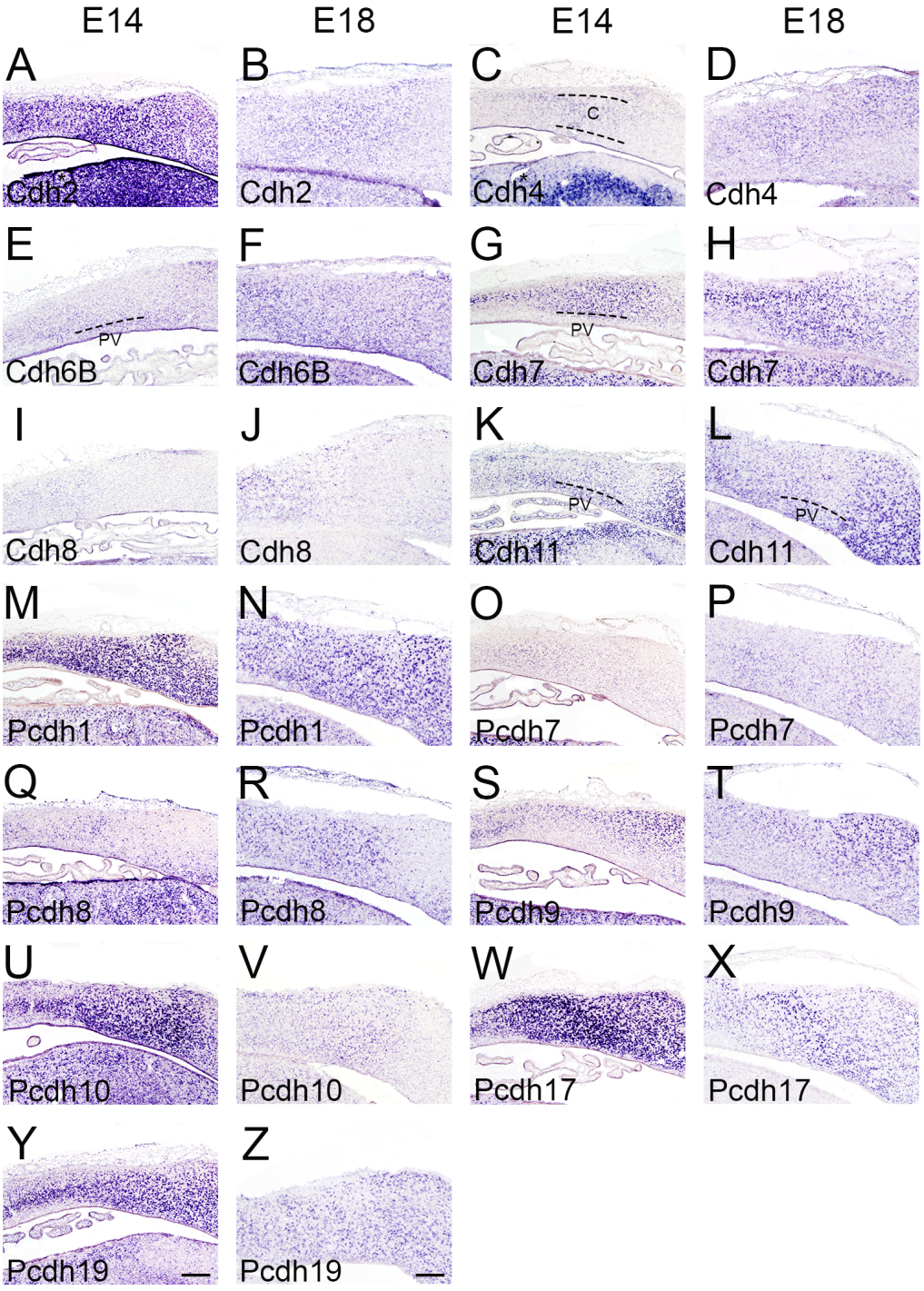

Fig. 6. Expression of cadherin mRNA in the APHi of developing chicken embryos at E14 and E18. (A, B) Cdh2. (C, D) Cdh4. (E, F) Cdh6B. (G, H) Cdh7. (I, J) Cdh8. (K, L) Cdh11. (M, N) Pcdh1. (O, P) Pcdh7. (Q, R) Pcdh8. (S, T) Pcdh9. (U, V) Pcdh10. (W, X) Pcdh17. (Y, Z) Pcdh19. S, the superficial layer; C, the cortical plate; PV, the periventricular layer. Dashed lines indicate the division between subregions and layers. The asterisks indicate artefacts. Scale bar=250 μm.

[31, 32]. The V-shaped region was proposed to be homologous to the dentate gyrus, the DM region (approximately corresponding to the APHm and APHi) was proposed to be homologous to Ammon's horn and the subiculum in mammals, and the DL region (approximately corresponding to the APHl) was proposed to be homologous to the entorhinal cortex [10, 12]. After checking the V-shaped region at E18, it was observed that Cdh2, Cdh8, Pcdh7, Pcdh8, Pcdh9, Pcdh17 and Pcdh19 expressed a moderate signal. Cdh4, Cdh6, and Cdh7 expressed a weak to moderate signal. Cdh11 and Pcdh1 showed strong expression, and the expression of Pcdh10 was weak (Fig. 3 and 4). Comparing cadherin expression in the V-shaped region and the APHm, the expression of Cdh2, Cdh8, and Pcdh8 were stronger in the V-shaped region than that in the APHm, and the expression of Pcdh10 was weaker

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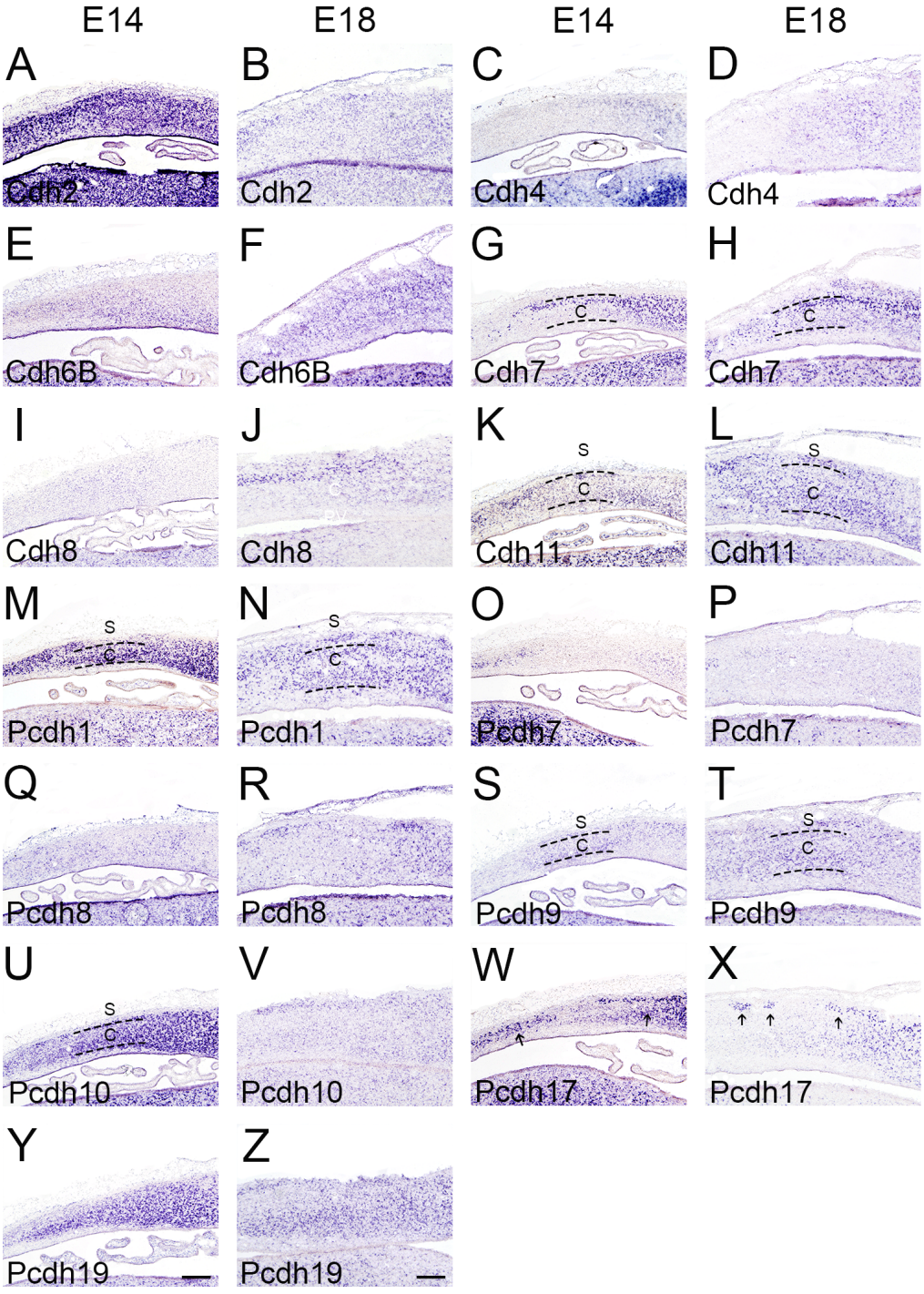

Fig. 7. Expression of cadherin mRNA expression in the APHl of developing chicken embryos at E14 and E18. (A, B) Cdh2. (C, D) Cdh4. (E, F) Cdh6B. (G, H) Cdh7. (I, J) Cdh8. (K, L) Cdh11. (M, N) Pcdh1. (O, P) Pcdh7. (Q, R) Pcdh8. (S, T) Pcdh9. (U, V) Pcdh10. (W, X) Pcdh17. (Y, Z) Pcdh19. S, the superficial layer; C, the cortical plate; PV, the periventricular layer. Arrowheads indicate the cell clusters. Dashed lines indicate the division between subregions and layers. Scale bar=250 μm.

in the V-shaped region (Fig. 3D, 3L and Fig. 4H, 4L). Comparing cadherin expression in the dentate gyrus and CA fields of mouse, similar expression was observed. The expression of Cdh2, Cdh8, and Pcdh8 was stronger in the dentate gyrus than that in CA fields (especially CA1), and the expression of Pcdh10 was weaker in the dentate gyrus (Fig. 9B, 9F, 9J, 9L).

DISCUSSION

APH in the developing avian embryo

Based on developmental gene expression, four avian pallial regions were identified: the medial pallium, the dorsal pallium, the lateral pallium, and the ventral pallium. In these four divisions, the medial pallium becomes the hippocampus formation. The dorsal

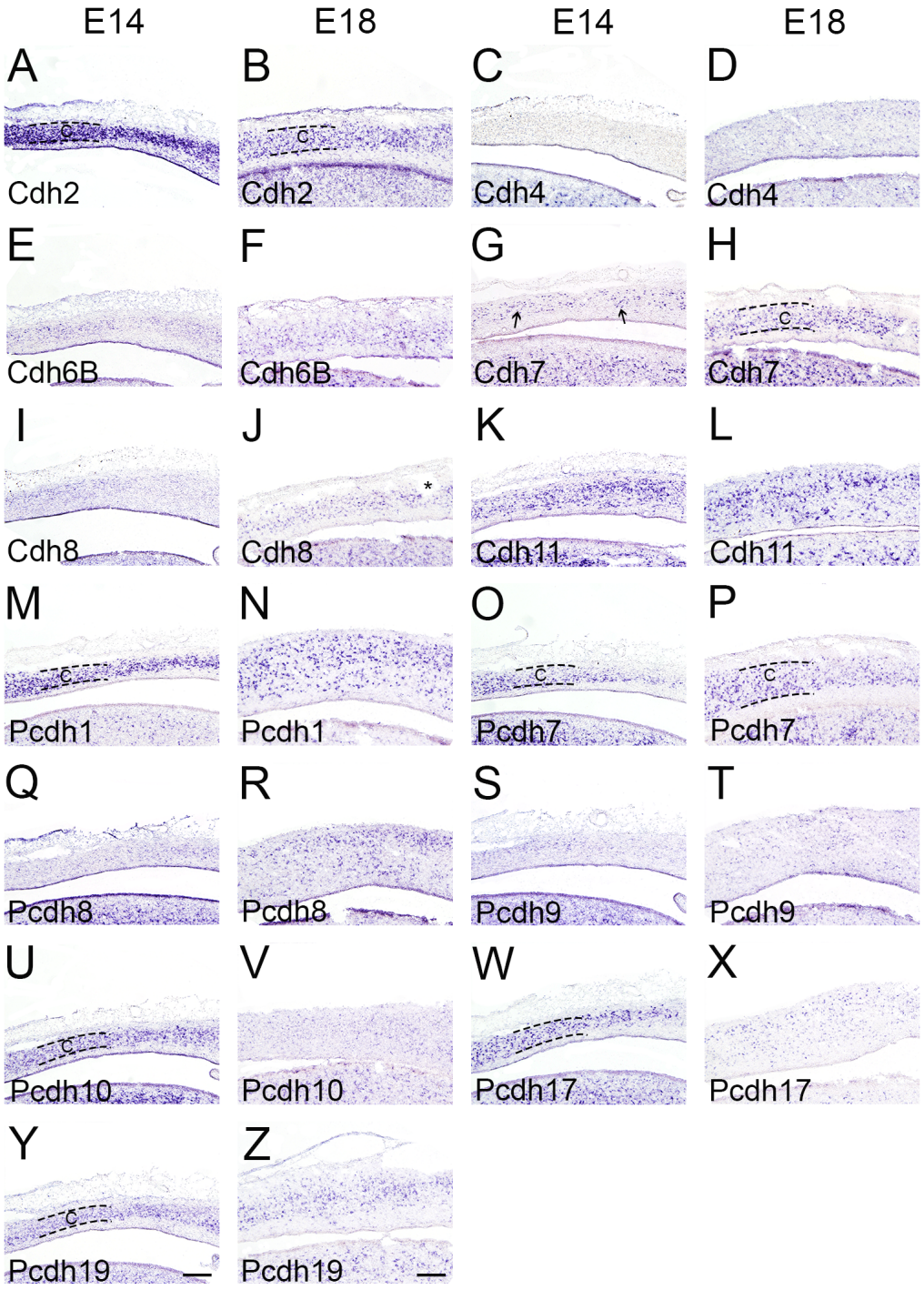

Fig. 8. Expression of cadherin mRNA expression in the APHcl of developing chicken embryos at E14 and E18. (A, B) Cdh2. (C, D) Cdh4. (E, F) Cdh6B. (G, H) Cdh7. (I, J) Cdh8. (K, L) Cdh11. (M, N) Pcdh1. (O, P) Pcdh7. (Q, R) Pcdh8. (S, T) Pcdh9. (U, V) Pcdh10. (W, X) Pcdh17. (Y, Z) Pcdh19. S, the superficial layer; C, the cortical plate; PV, the periventricular layer. Arrowheads indicate the scattered cells. Dashed lines indicate the division between subregions and layers. The asterisks indicate artefacts. Scale bar=250 μm.

pallium becomes the hyperpallium (the Wulst). The lateral pallium and ventral pallium develop into the dorsal ventricle ridge (DVR), which includes the nidopallium, mesopallium, and archistriatum [33-36]. For the medial pallium, although functional similarity exists with the mammalian hippocampus [37], it is still difficult to define the boundaries between the different subregions of the avian hippocampal formation despite the ease of distinguishing the subdivisions of the mammalian hippocampus, such as the dentate gyrus and Ammon's horn [2]. Various schemes of the avian hippocampal formation have been proposed. Wild et al. defined the avian hippocampal formation as the hippocampus and APH [19]. Based on tract tracing, Kahn et al. defined the hippocampal formation as the V-shaped medial area, the APH, and a thin structure overlying the dorsolateral ventricle [8]. Soon after, Atoji et al.

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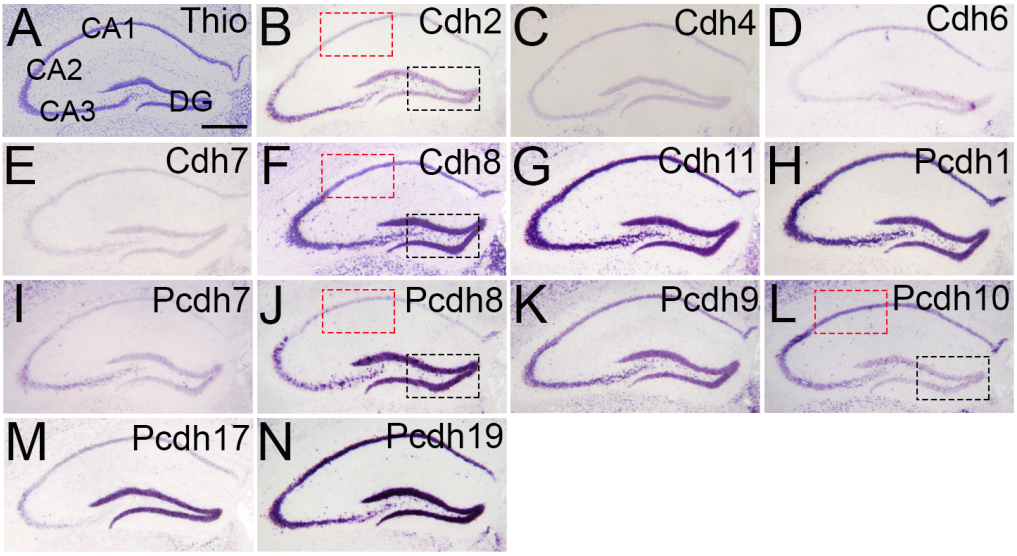

Fig. 9. Expression of cadherin mRNA expression in the hippocampus of adult wild-type mice. (A) Thionin staining for anatomical structure. (B~N) Classic cadherin and protocadherin molecules. CA1-CA3, CA fields of hippocampus. DG, dentate gyrus. (B, F, J, L). Red dashed line, CA1; Black dashed line, DG. Scale bar=500 μm.

introduced a new division that mainly included the dorsal and ventral portions of the DL, the medial and lateral portions of the DM, the V-shaped structure and the triangular region [10, 38]. A study on Cdh4, Cdh6 and Cdh7 expression using immunohistochemistry performed previously provided a scheme that included four subdivisions (APHm, APHi, APHl, APHcl) [12, 39]. By using neurochemical markers, researchers found that the APHi can be further divided into medial and the lateral subdividsions [40]. Our *in situ* hybridization results from different cadherins also support these schemes. Some cadherin mRNAs displayed borders between the subregions, such as Cdh7, Cdh11, Pcdh1, Pcdh10, and Pcdh17 (Fig. 3 and 4). Cdh11 and Pcdh7 displayed a boundary between the medial and lateral portion of the APHi (Fig. 5L and 5P). The results of Pcdh8 and Pcdh9 in the APHm indicate that the periventricular layer of APHm corresponds to the lateral layer of the V-shaped structure defined by Atoji and Wild [2] on a cytoarchitectural basis (Fig. 5R and 5T).

Regional expression of cadherin mRNAs in subdivisions of the developing APH

The expression of cadherins in chicken embryos has been mapped and reported by different groups [30, 39, 41-43]. In the chicken embryonic brain, the expression and regulation of cadherins was studied during development [44-46]. However, except for a few molecules, the profile of cadherins in APH has not been systemically described.

Expression of cadherins varies temporally and spatially in subregions of chicken APH. Several cadherin molecules have displayed layered expression, especially in APHl (Cdh7, 8, 11, Pcdh1, 9, 17). In our study, a transitional border could be observed between chicken APHl and APHcl in the expression of most cadherins, such as Cdh4, Cdh7, Cdh8, Pcdh1, Pcdh7, Pcdh8, Pcdh9, Pcdh10, Pcdh17, and Pcdh19 (Fig. 7 and 8), which may offer a molecular basis for dividing these two parts. Our previous findings of patches in Pcdh17 expression suggest that there may be a similar cytoarchitectural basis in the outer layer of APHl, as seen in APHcl [11]. This phenomenon may be explained by the cadherin-dependent cell segregation mechanism proposed by previous researchers, which could influence the formation of brain nuclei and cortical regions and layers [38, 47, 48].

These results that the expression of cadherin mRNA was diversified during development may indicate that some cadherins are integral to the development of the chicken hippocampal formation and involved in the establishment of recognition functions [11, 12]. Various expression patterns of cadherins in APH may prove that cadherins play roles in specific regional development of APH subdivisions [7, 49, 50].

Possibility of cadherins involved in APH evolution

Siegel et al. [51] found that neurons in the ventral hippocampal formation of avian species displayed similar activity patterns to cells in Ammon's horn in mammals and neurons in the dorsocaudal area of the avian hippocampal formation to the dentate gyrus in mammals using an electrophysiological technique [38, 52, 53]. Kahn et al.'s study [8] proposed that the ventral layer of the V-shaped region in avian species was homologous to Ammon's horn in mammals and that the DM region was homologous to the dentate gyrus [33, 54].

In APH, the subdivisions of APHm and APHi correspond to the DM subregion of Atoji and Wild's division [10] of the APH. APHl

corresponds to the DL subregion of Atoji and Wild's division, and APHcl corresponds to the extension of the superficial part of the dorsolateral corticoid lateral area [11, 47]. According to Atoji and Wild [2, 10], the boundary between DL and CDL subdivisions was not clearly defined. Our results that APHl and APHcl could be divided by some cadherins, Cdh4, Cdh7, Cdh8, Pcdh1, Pcdh7, Pcdh8, Pcdh9, Pcdh10, Pcdh17, and Pcdh19, provided a possible border between DL and CDL from Atoji and Wild's division. The changing expression of Cdh2, Cdh7, Cdh8, Cdh9, Cdh12, Pcdh1, Pcdh7, Pcdh8, Pcdh9, Pcdh10, Pcdh15, Pcdh17 and Pcdh19 at E14 and E18 indicates that they might be involved the APH development in chickens.

In the current study, we compared the expression of cadherin mRNAs in the subregions of E18 chicken embryos with wild-type adult mice. The cadherin molecules with special regional expression at E14 and E18 indicate that they may play roles in avian hippocampal development, and the layer specificity of these molecules suggests they may be integral to neurogenesis specifically [11, 55-57]. The layer specificity of cadherin expression was also be observed in the lateral entorhinal cortex of the mouse [44, 45, 58, 59]. In wild-type adult mice and the corresponding E18 chicken embryo APH subregions (dentate gyrus in mouse and V-shaped region in chicken), many cadherin molecules, such as Cdh2, Cdh4, Cdh6, Cdh7, Cdh11, Pchd1, Pcdh7, Pcdh9 and Pcdh10, showed similar regional expression. Our results regarding the changes between different subregions indicate that Cdh2, Cdh8, Pcdh8 and Pcdh10 might have regionally homologous expression in chicken and mouse hippocampal formations. This is consistent with Cindrova-Davies' research [60] on the functionally conservation of yolk sac among human, mouse and chicken [61]. Similarly, the complicated brain has its own evolutionary mechanism and conserved genetic system. As special markers, these genes may be useful in studying the differentiation of the avian hippocampal formation to reveal the mechanism of hippocampal development and evolution [41, 62-64].

ACKNOWLEDGEMENTS

This work was supported by the Anatomy I Institute of the University of Jena. The author thanks Dr. Kaether, Prof. Dr. Jucker, and Prof. Dr. Haass and their groups for the mouse model and antibodies and Dr. F. van Roy, Dr. M. Takeichi, Dr. T. Jessell and Dr. H. Cremer for some plasmids. All authors participated in this study and have access to all data in this work. This work was supported by the National Natural Science Foundation of China, Grant/Award Number: 81401015, and the Foundation of Birth Defect Prevention Key Laboratory, National Health Commission of the People's Republic of China, Grant/Award Number: ZD201901.

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