Chapter 2
Developmental Alteration of Hypocretins (Orexins) in the Brainstem in the Sudden Infant Death Syndrome

Yuri Ozawa, Sachio Takashima, Hiroko Nonaka, and Naoki Uga

Abstract *Objective:* The hypocretins (orexins) (HCRT), which help regulate aspects of sleep and wakefulness, are synthesized by neurons located exclusively in the lateral hypothalamus. Hcrt-containing neurons project throughout the CNS and project especially heavily to the noradrenergic locus coeruleus (LC). Sudden infant death syndrome (SIDS) remains the principal cause of postneonatal infant death, but mechanisms underlying the syndrome have not been completely elucidated. Recently, failure to arouse from sleep has been suggested as contributing to SIDS. Therefore, we studied developmental changes in HCRT-1 and HCRT-2 in the brainstem and compared those changes between SIDS cases and controls. *Methods:* Twenty cases of SIDS and 21 controls, aged from 20 gestational weeks to 13 years of age, were selected. We examined the brainstems of each subject for HCRT-1 and HCRT-2 with immunohistochemistry techniques. *Results:* HCRT-1 appeared in the brainstem from the early fetal period. Its expression was moderately present at 6 months in the LC, dorsal raphe nucleus (DRN), and periaqueductal gray matter

Y. Ozawa (✉)
Department of Neonatology, School of Medicine, Toho University,
6-11-1 Ohmorinishi, Ohta, Tokyo 143-8541, Japan

Shimada Ryoiku Center Hachiouji (Institution for Persons with Severe Motor and Intellectual Disabilities), Tokyo, Japan
e-mail: yurioz@med.toho-u.ac.jp

S. Takashima
Yanagawa Institution for Development Disabilities,
Internal University of Health and Welfare, Yanagawa, Fukuoka, Japan

H. Nonaka
Department of Surgical Pathology, Ohmori Hospital,
School of Medicine, Toho University, Tokyo, Japan

N. Uga
Department of Neonatology, School of Medicine, Toho University,
6-11-1 Ohmorinishi, Ohta, Tokyo 143-8541, Japan

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(PAG) and then gradually increased during development. HCRT-2 was detected from the neonatal period in the medulla oblongata and LC and from the early fetal period in the DRN and PAG, respectively. Its expression gradually increased from 6 months in the LC, DRN, and PAG. We found intense expression of HCRT-1 in the LC in the SIDS victims earlier than in the controls. No definitive developmental changes emerged in immunoreactivity of HCRT-2 between SIDS cases and controls in the brainstem. *Conclusions.* This study revealed developmental alterations in HCRT-1, a peptide related to arousal, in the LC of SIDS victims relative to controls, suggesting that the hypothalamic-pontine hypocretinergic system is involved in the pathophysiology of SIDS.

Keywords Development • Hypocretin (orexin) • Immunohistochemistry • LC • SIDS

Abbreviations

CNS	Central nervous system
CSF	Cerebrospinal fluid
DRN	Dorsal raphe nucleus
HCRT	Hypocretin
LC	Locus coeruleus
LDT	Laterodorsal tegmental nucleus
REM	Rapid eye movements
SIDS	Sudden infant death syndrome

2.1 Introduction

The campaign for placing infants in the supine state during sleep has reduced the incidence of sudden infant death syndrome (SIDS) [1, 2], but SIDS remains the principal cause of postneonatal infant death. The mechanisms underlying SIDS have not been completely elucidated.

SIDS is defined as the sudden death of an infant under 1 year of age that remains unexplained after a complete clinical review, autopsy, and death scene investigation [3]. SIDS occurs in infants less than 1 year of age, with a peak incidence at 2–4 months of age, and appears as an unexpected event during sleep. These characteristics suggest that SIDS results from impaired sleep development and cardiorespiratory regulatory areas.

Previous studies on the brain have revealed high incidences of leukomalacia [4], gliosis in respiratory areas of the brainstem [5–7], developmental delay of dendritic spines and synapses [8–10], and altered myelination in the brainstem [11]. Failure to arouse from sleep has been suggested to contribute to SIDS [12], and the syndrome likely develops from a compromised arousal response from a breathing or blood pressure challenge during sleep.

The hypothalamic neuropeptides hypocretin (HCRT)-1 and HCRT-2 (also named orexin-A and orexin-B) have been recently identified and are synthesized solely in the lateral hypothalamus and adjacent regions [13, 14]. The peptides are derived from the same long 130-amino-acid prepro-hypocretin molecule through proteolytic cleavage [14]. HCRT-1 is a 33-amino-acid peptide with an N-terminal pyroglutamyl residue and a C-terminal amide, while HCRT-2 is a 28-amino-acid peptide with a C-terminal amide [14]. HCRT-2 has been reported to exhibit 46 % similarity with HCRT-1 [14]. Both peptides bind and activate G protein-coupled receptors [13, 14]. Recent evidence suggests that both peptides participate in the regulation of behavioral arousal [15]. In animals, intracranial administration of HCRT increases wakefulness [16–20]. Human narcoleptic patients show low or undetectable levels of HCRT in the cerebrospinal fluid [21] and a loss of HCRT neurons [22]. The mechanisms by which HCRT regulates the state of arousal are not well understood. HCRT-synthesizing neurons project profusely into regions involved in the regulation of sleep-wake behavior, including the dorsal raphe nucleus (DRN), locus coeruleus (LC), laterodorsal tegmental nucleus (LDT), and pedunculo-pontine tegmental nucleus [23]. HCRT excites noradrenergic LC [16, 24, 25] and serotonergic DRN [26] neurons and may promote wakefulness by elevating monoaminergic tone [15]. HCRT-1 microinjection into the cat pontine reticular formation triggers REM sleep [27], suggesting that HCRT-1 may also promote brain activation by enhancing pontine cholinergic neurotransmission [15]. In this study, the primary finding was developmental changes in HCRT-1 and HCRT-2 intensities in the brainstem; a secondary finding, demonstrated by immunohistochemical methods, was a developmental difference in HCRT-1 and HCRT-2 intensities between SIDS victims and controls.

2.2 Patients and Methods

We selected 21 control cases aged from 20 gestational weeks to 13 years of age. The clinical diagnoses of the controls are shown in Table 2.1. There were no pathological findings such as hypoxic-ischemic changes in the brainstem. Twenty cases of SIDS were selected according to a clinical history of sudden death or unexpected death and a failure to reveal a cause of death on autopsy and death scene investigation. The diagnosis of SIDS was based on the international pathologic criteria for SIDS. The cases consisted of 4 term neonates and 16 infants aged from 1 to 8 months. The cases were all Japanese. Written informed consent for autopsy was obtained for all cases, and autopsies were performed within 24 h of death. There were no significant differences in the time from death to autopsy between the SIDS cases and controls. First, we examined developmental changes in HCRT-1 and HCRT-2 intensity in the solitary, dorsal vagal nucleus and hypoglossal nuclei in the medulla oblongata, LC in the pons, and DRN and periaqueductal gray matter (PAG) in the midbrain. Developmental differences were then compared in these structures between SIDS victims and controls by immunohistochemical methods. The studies were performed blind as to the diagnosis.

Table 2.1 Clinical diagnoses of the control cases

Patient no.	Gestational weeks	Postnatal age	Clinical diagnosis
1	20		ELBW, RDS, pulmonary hemorrhage
2	22		ELBW, RDS, shock
3	23		ELBW, pulmonary hypoplasia
4	25		ELBW, TTTS, RDS
5	29		Potter syndrome
6	32		Pulmonary valve hypoplasia
7	36		Potter syndrome
8	37		LBW, tetralogy of Fallot, malrotation
9	40		MAS, PPHN
10	42		Severe asphyxia
11		1 month	Postoperative aortic atresia
12		3 months	Pierre–Robin syndrome
13		3 months	Hirschsprung disease
14		5 months	Hirschsprung disease
15		6 months	Klippel–Weber syndrome
16		10 months	Holt–Oram syndrome
17		1 year	Single ventricle
18		5 years	Primary pulmonary hypertension
19		5 years	Acute myeloblastic leukemia
20		10 years	Acute lymphocytic leukemia
21		13 years	Acute lymphocytic leukemia

ELBW extremely low birth weight infant, *RDS* respiratory distress syndrome, *TTTS* twin-to-twin transfusion syndrome, *MAS* meconium aspiration syndrome, *PPHN* persistent pulmonary hypertension of the newborn

Tissues for conventional examination were dissected from the cerebral hemispheres, which included the basal ganglia and thalamus, cerebellar hemispheres and vermis, midbrain, pons, and medulla oblongata, fixed in formalin or paraformaldehyde, embedded in paraffin, and then cut into 4-μm-thick sections. The sections were stained with hematoxylin and eosin. Then, sections were subjected to routine neuropathological examination. For the brainstem, we selected three levels: the middle level of the midbrain, which contained the superior colliculus and oculomotor nucleus, the upper level of the pons, which contains the decussation of trochlear nerves, and the middle level of the medulla oblongata [28, 29].

The sections for immunohistochemistry with HCRT-1 and HCRT-2 antibodies were deparaffinized and pretreated with 0.3 % hydrogen peroxide in methanol for 20 min and then subjected to microwave irradiation and rinsing with a phosphate buffered solution (PBS) (pH 7.4). They were then preincubated in the presence of 10 % normal goat serum for 30 min and incubated with rabbit polyclonal antibodies against HCRT-1 and HCRT-2 (Peninsula Laboratories Inc.) diluted 1:1,000 overnight at 4 °C, followed by biotinylated goat anti-rabbit IgG (Nichirei) for 1 h, and then stained with peroxidase-conjugated streptavidin (Nichirei) for 30 min at room temperature. Each step was followed by washing in PBS with 0.3 % Triton-X. The immunoproducts were visualized using 0.02 M diaminobenzidine

tetrahydrochloride as the chromogen in 0.05M Tris buffer, pH 7.4, containing 0.006 % hydrogen peroxide.

The presence of HCRT-1 and HCRT-2 immunoreactivity in the brainstem was determined visually using the following four-category rating scale: negative (–), very sparse (mild) (+), sparse (moderate) (++), and dense (marked) (+++).

2.3 Results

2.3.1 Normal Expression of HCRT-1 and HCRT-2 in the Brainstem

HCRT-1 was observed in the brainstem from the early fetal period. In the medullary solitary, dorsal vagal and hypoglossal nuclei, no definitive developmental changes appeared. HCRT-1 expression was moderately detected at 6 months in the pontine LC, and midbrain DRN and PAG, and then gradually increased during development (Table 2.2).

HCRT-2 was detected from the neonatal period in the solitary, dorsal vagal and hypoglossal nuclei, and LC in the pons, whereas in the midbrain DRN and PAG, the peptide was observed from the early fetal period. In the medullary solitary, dorsal vagal and hypoglossal nuclei, no definitive developmental changes appeared. HCRT-2 expression gradually increased from 6 months in the LC in the pons and DRN and PAG in the midbrain (Table 2.3).

2.3.2 Comparison of HCRT-1 and HCRT-2 Immunoreactivity Between SIDS Cases and Controls (Fig. 2.1)

There were no definite developmental changes in the immunoreactivity of HCRT-1 betweeten SIDS cases and controls in the medulla oblongata and midbrain. However, in the pontine LC, immunoreactivity to HCRT-1 in SIDS cases was detected moderately and markedly 2 months earlier than in controls (Table 2.2).

There were no definite developmental changes in immunoreactivity of HCRT-2 between SIDS cases and controls in the brainstem (Table 2.3).

2.4 Discussion

In this study, we examined the developmental changes in HCRT-1 and HCRT-2 in the brainstem and compared the developmental expression between SIDS cases and controls with immunohistochemical techniques. We found earlier intense expression of HCRT-1 in the LC in the SIDS victims than in controls.

Table 2.2 Developmental changes in HCRT-1 immunoreactivity in the brainstem in SIDS and control cases

			Medulla oblongata						Pons		Midbrain			
	N		Solitary nucleus		Dorsal vagal nucleus		Hypoglossal nucleus		LC		DRN		PAG	
Age	Control	SIDS	Control	SIDS	Control	SIDS	Control	SIDS	Control	SIDS	Control	SIDS	Control	SIDS
20–22 GW	2		−		−		−		−		+		+	
23–27 GW	2		−		−		−		−		+		+	
28–31 GW	1		−		−		−		−		+		+	
32–36 GW	2		−		−		−		+		+		+	
37–42 GW	3	4	+	+	+	+	+	+	+	+	+	+	+	+
0–1 M	1	2	+	+	+	+	+	+	+	+	+	+	+	+
2–5 M	3	11	+	+	+	+	+	+	+	+	+	+	+	+
6–11 M	2	3	+	+	+	+	+	+	++	+~++	+~++	+	+~++	+
1–5 Y	3		+		+		+		++~+++		+~++		+~++	
6–13 Y	2		+		+		+		++~+++		+~++		++	

GW gestational weeks, *M* months, *Y* years, *HCRT* hypocretin, *SIDS* sudden infant death syndrome, *LC* locus coeruleus, *DRN* dorsal raphe nucleus, *PAG* periaqueductal gray matter

Table 2.3 Developmental changes in HCRT-2 immunoreactivity in the brainstem in SIDS and control cases

			Medulla oblongata						Pons		Midbrain			
	N		Solitary nucleus		Dorsal vagal nucleus		Hypoglossal nucleus		LC		DRN		PAG	
Age	Control	SIDS	Control	SIDS	Control	SIDS	Control	SIDS	Control	SIDS	Control	SIDS	Control	SIDS
20–22 GW	2		−		−		−		−		+		+	
23–27 GW	2		−		−		−		−		+		+	
28–31 GW	1		−		−		−		−		+		+	
32–36 GW	2		−		−		−		+		+		+	
37–42 GW	3	4	+	+	+	+	+	+	+	+	+	+	+	+
0–1 M	1	2	+	+	+	+	+	+	+	+	+	+	+	+
2–5 M	3	11	+	+	+	+	+	+	+	+	+	+	+	+
6–11 M	2	3	+	+	+	+	+	+	++	+~++	+~++	+	+~~++	+
1–5 Y	3		+		+		+		++~+++		+~++		+~++	
6–13 Y	2		+		+		+		++~+++		+~++		++	

GW gestational weeks, *M* months, *Y* years, *HCRT* hypocretin, *SIDS* sudden infant death syndrome, *LC* locus coeruleus, *DRN* dorsal raphe nucleus, *PAG* periaqueductal gray matter

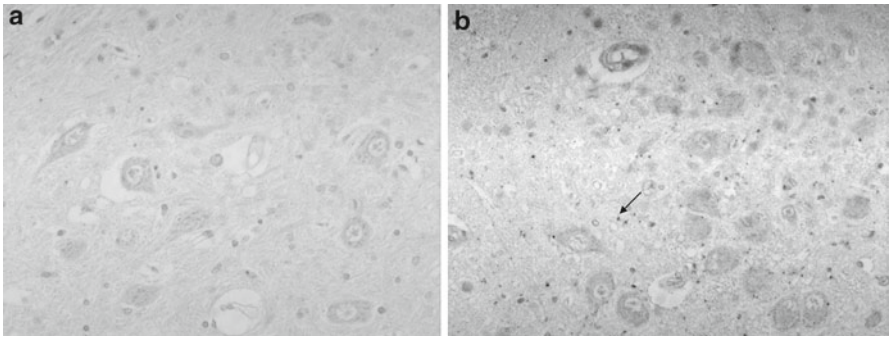

Fig. 2.1 HCRT-1 immunoreactivity in the LC. Immunoreactive fibers are very sparse in a control case at 2 months of age (**a**) and sparse in a SIDS case at 2 months of age (*arrow*) (**b**). Original magnification, ×100

Several reports demonstrate that HCRT acts in the central nervous system to modulate feeding, sleep–wakefulness, neuroendocrine homeostasis, and autonomic regulation [14, 30, 31]. HCRT-containing neurons, which are located exclusively within the lateral hypothalamus [14, 23, 32], project to a large number of neuronal loci in the brain and spinal cord [23], involving arousal-promoting brainstem nuclei, including the DRN, LC, and pontine reticular nucleus; particularly strong innervation is present in the LC [24].

Both HCRT-1- and HCRT-2-labeled fibers are located in the same regions in the cat brainstem [33]. In addition, the density of HCRT-2-labeled fibers is less than that of HCRT-1-labeled ones in most regions that contain both [33]. We also found both peptides in the human brainstem. In the rat brain, some studies have revealed developmental changes in HCRT by means of immunohistochemistry [34, 35] and by mRNA on Northern blot analysis [36] and in situ hybridization [37]. According to Yamamoto et al., HCRT-1 and HCRT-2 immunoreactive cells and fibers are not detected in the hypothalamus from days 0 to 10, but present at day 15, and then markedly increase between postnatal days 15 and 20 [34]. Steininger et al. founded that HCRT mRNA and protein are not detected until embryonic day 18 (E18), and at P16, HCRT immunoreactive cell bodies are similar to those in adults. HCRT immunoreactive processes are first observed in the hypothalamus at E20 and are also slightly evident in the LC. During early neonatal development, the number of labeled fibers increases. The density in the LC progressively increases throughout the early postnatal period, reaches peak levels at P21, and then remains at the same level as in adulthood [37]. Whereas in humans, in infants under 4 months, lumbar cerebrospinal fluid HCRT-1 levels are similar to those in adults [38].

During development, the pattern of sleep/waking activity also undergoes a dramatic change. Slow waves that occur during non-REM sleep are first detected by electroencephalography by P10-11, but the light-dark pattern of sleep remains undifferentiated until around P20, when the adult-like pattern begins to emerge. The adult-like pattern is established by P24, although adult levels of sleep amount

are not established for several weeks [39, 40]. Thus, since development of HCRT coincides with establishing sleep-patterns, HCRT may be involved in the postnatal changes in sleep/wakefulness states.

HCRT binds two guanine nucleotide binding protein (G protein)-coupled receptors, hypocretin-1 receptor (HCRT-R1) and HCRT-R2 [14]. HCRT-R1 shows a higher affinity for HCRT-1 than for HCRT-2; whereas, HCRT-R2 shows equally high affinity for the two peptides [14]. The LC primarily expresses HCRT-R1 [14, 17]. Bernard et al. demonstrated that activation of HCRT receptors stimulates G proteins in arousal-related brainstem nuclei [41]. Direct administration of HCRT to the pontine brainstem increases either wakefulness or REM sleep, depending on the nucleus involved. Microinjection of HCRT-1 into the rat LC [17] increases wakefulness and suppresses REM sleep, reflecting the potential importance of the HCRT projection to the LC. Recently, it was suggested that HCRT-1 may exert an effect on neuronal circuits that control the autonomic nervous system [30, 42].

The LC provides noradrenergic innervation to many regions of the brain. Functionally, the LC plays important roles in direct attention and arousal/sleep modulation [17]. Through a noradrenergic innervation, the LC plays important roles in targeting attention and modulating the level of awareness. The LC develops early and may play a role in modulation of the development of other neuronal loci that it innervates. The output of the LC may be important developmentally in regulation of the arousal state. While noradrenergic neurons appear quite early, axonal extension and terminal field elaboration occur throughout the postnatal developmental period and peak at a similar age to HCRT in most brain regions, suggesting a relation between the noradrenergic diffuse ascending projection system and HCRT development [43–45]. HCRT directly activates receptors on the postsynaptic membranes of LC neurons to increase the frequency of action potentials [24]. Together with the frequent synapses found between HCRT axons and LC neurons, HCRT axons projecting from the lateral hypothalamus may enhance activity of the LC noradrenergic system [24, 46]. Van den Pol et al. suggested that the hypothalamus, via HCRT projections, may be able to enhance arousal and modulate plasticity in higher centers through the developing LC [47]. Alterations in sleep architecture induced by HCRT-1 may be the consequence of a neuroexcitatory effect on LC neurons through HCRT-R1 [17].

We showed intense HCRT-1 immunoreactivity in the LC of SIDS cases from 2 months of age, i.e., earlier than in controls. Multiple neurotransmitter systems in the brainstem are involved in the control of behavioral states of sleep and wakefulness. Our previous studies did not find alterations in neurotransmitters and their receptors in the LC of SIDS cases. Further studies are required to determine the means whereby hypocretinergic projections to the LC interact with these neurotransmitter systems; such studies may assist in revealing the mechanism of SIDS. The present data indicate that a hypothalamic-pontine hypocretinergic system may be involved in the pathophysiology of SIDS.

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