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Interleukin-1β and its Type 1 Receptor Are Expressed in Developing Neural Circuits in the Frog, *Xenopus laevis*

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ABSTRACT

The cytokine interleukin-1 beta (IL-1β) is an evolutionarily conserved molecule that was originally identified in the immune system. In addition to regulating peripheral immune responses, IL-1β plays an important role in mediating neural-immune interactions and regulating glial activities during healing and repair in the damaged nervous system. Active IL-1β is produced by interleukin-converting enzyme (ICE), a caspase thought to be involved in the induction of apoptosis. We report that, in the developing frog, *Xenopus laevis*, IL-1β and the IL-1 type 1 receptor proteins are coexpressed in specific neurons that comprise early sensory-motor circuits. IL-1β and IL-1 type 1 receptor proteins are colocalized in specific midbrain and hindbrain reticular cells, including Mauthner's neuron; specific cells in the trigeminal (fifth), lateral line (seventh), and vestibular (eighth) cranial ganglia; oculomotor neurons; and the primordial Purkinje cells of the lateral cerebellar auricle. In the spinal cord, Rohon-Beard sensory neurons, dorsal root ganglion cells, and primary motoneurons are immunopositive. Anteriorly, the olfactory pits, olfactory nerves, and olfactory bulbs are labeled, as are retinal cells, especially photoreceptor inner segments. With regard to the function of IL-1β during neural development, IL-1β and its type 1 receptor are present throughout the course of neural development in identifiable, long-lived neurons, such as Mauthner's neuron. These and other data suggest that IL-1β and its type 1 receptor may be involved in the maintenance of cell survival rather than induction of neuronal death. J. Comp. Neurol. 394:242–251, 1998.

Indexing terms: cytokine; amphibian; Mauthner neuron; identified neurons; neuronal survival

Cytokines are ubiquitous molecules that are known classically for their ability to regulate the immune system (Benveniste, 1992). Although they were originally identified in the immune system, cytokines are present in both the adult and the developing nervous systems. Cytokines play an integral role in mediating neural-immune interactions (Araujo and Cotman, 1995; Rothwell and Strijbos, 1995; Sei et al., 1995) and neuroendocrine interactions (Besedovsky et al., 1991; Benveniste, 1992; Del Rey et al., 1996).

In the developing nervous system, cytokines can influence cell growth, differentiation, and survival (Merrill, 1992; Berezovskaya et al., 1995; Sawada and Marunouchi, 1995; Michaelson et al., 1996). For example, leukemia-inhibitory factor (LIF) and interleukin 6 (IL-6) are expressed in specific subpopulations of cells in a spatiotemporal pattern in the developing brain (Gadient and Otten, 1994; Pousset, 1994; Qui et al., 1994). LIF influences survival and/or differentiation of several classes of neurons and synapse withdrawal in neonatal muscles of the mouse (Patterson and Nawa, 1993; Kwon et al., 1995). IL-6 also promotes the survival of specific neurons during development and induces expression of nerve growth factor (NGF; Hama et al., 1989). Insulin-like growth factor (IGF) and transforming growth factor beta (TGF-β) also promote survival in developing motoneurons (Martinou et al., 1990; Neff et al., 1993; Oppenheim et al., 1993).

The cytokine interleukin-1 beta (IL-1β) is constitutively expressed in the developing mouse brain (Scripter et al.,

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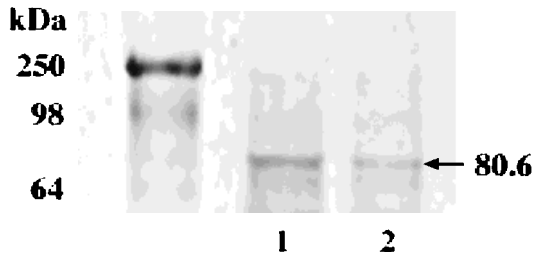

Fig. 1. Western blot shows that a polyclonal interleukin-1 type 1 (IL-1 type 1) receptor antibody recognizes a putative *Xenopus laevis* IL-1 type 1 receptor protein with a molecular weight of 80.6 kDa. The mammalian IL-1 type 1 receptor protein has a molecular weight of 80 kDa. Protein from 5-day-old *Xenopus laevis* tadpoles were run in lanes 1 and 2.

TABLE 2. IL-1β Immunoreactivity in Other Neural Structures[1]

Age (days)	N	Cranial nerves I	Cranial nerves II	Retina	Optic and cranial muscles	Hypothalamus	Cerebellum
2	17	94	100	94	100	94	94
3	15	80	93	87	100	73	100
4	19	95	100	74	100	90	79
5	17	89	100	100	100	88	82
6	14	100	100	93	100	100	93
7	12	83	100	92	100	92	92
8	12	100	75	92	100	100	92
9	6	67	100	100	100	100	83
10	10	90	100	100	100	100	90
11	8	100	100	100	100	75	100
12	8	88	88	88	88	75	63

[1]Total numbers of animals analyzed per day of development are listed above. Animals were scored for the presence of IL-1β immunoreactivity, which is represented as a percentage of the total number of animals scored for that day of development.

TABLE 1. Interleukin-1 Beta Immunoreactivity in Sensory and Motor Structures That Comprise Locomotor Circuits[1]

Age (days)	Total animals (n)	Cranial ganglia Fifth	Cranial ganglia Seventh	Cranial ganglia Eighth	Reticular cells Mauthner's	Reticular cells Hindbrain	Reticular cells Midbrain	Tail structures RB/MN	Tail structures DRG	Tail structures Muscle
2	17	100	100	100	76	94	71	76	0	94
3	15	100	93	93	100	100	87	73	100	
4	17	100	100	94	76	100	88	94	88	100
5	17	100	94	94	100	82	88	59	100	
6	14	100	100	79	93	86	50	100	93	100
7	12	100	100	92	75	100	75	100	100	100
8	12	100	100	100	75	100	58	100	92	100
9	6	100	100	100	100	100	50	100	67	100
10	10	90	90	70	70	100	50	100	60	100
11	8	100	100	100	75	100	13	100	100	100
12	8	100	100	88	75	88	50	100	100	100

[1]Total numbers of animals analyzed per day of development are listed above. Animals were scored for the presence of interleukin-1 beta (IL-1β) immunoreactivity, which is represented as a percentage of the total number of animals scored for that day of development. RB, Rohon-Beard neurons; MN, Mauther's neurons; DRG, dorsal root ganglia.

1997). Although a few studies have shown that IL-1 can influence cell survival, its role in the developing nervous system has not yet been elucidated (Brenneman et al., 1992, 1995). The role of IL-1β as a neural-immune molecule in the adult nervous system, however, is well established. IL-1β is produced by astrocytes, microglia, and neurons (Giulian et al., 1986; Breder et al., 1988) and is up-regulated in response to injury, trauma, or endotoxin treatment (Dinarello, 1991; Minami et al., 1992; Gatti and Bartafi, 1993). IL-1β is involved in regulating healing and/or repair in both the developing and the adult nervous systems (Giulian and Lachman, 1985; Giulian et al., 1986, 1988b; Rothwell and Strijbos, 1995; Scripter et al., 1997).

In this paper, we demonstrate that IL-1β and the IL-1 type 1 receptor are expressed in a distinct pattern in the nervous system of the developing frog, *Xenopus laevis*. Neurons that comprise classically defined locomotor circuits display rich IL-1β and IL-1 type 1 receptor immunoreactivity. These structures include the fifth, seventh, and eighth cranial ganglia; Mauthner's giant neuron; primary motoneurons; and tail myotomes. In addition, among others, the Rohon-Beard sensory neurons, dorsal root ganglia, and reticular cells of the midbrain and hindbrain are immunoreactive.

MATERIALS AND METHODS

Animals

All animals were treated in accordance with an animal use protocol approved by the Institutional Animal Care and Use Committee of Tulane University. Embryos were obtained by injecting adult *Xenopus laevis* frogs with human chorionic gonadotropin (Sigma Chemical Co., St. Louis, MO). Fertilized eggs were separated into plastic containers containing charcoal-filtered tap water and were staged according to Nieuwkoop and Faber (1994). Tadpoles from day 2 (stage 32/33) through day 12 (approximately stage 49) of development were collected, fixed in Bouin's solution, and embedded in paraffin blocks. Twenty-micrometer horizontal or coronal sections were cut on a microtome and heated onto gelatin-coated slides.

Immunocytochemistry

The tissue was deparaffinized in xylene, rehydrated through a series of graded alcohols and washed in phosphate-buffered saline (PBS), pH 7.4. Tissue sections were quenched in a 2% hydrogen peroxide (H_2O_2) solution for 5 minutes followed by a 2-hour incubation in blocking solution (IL-1β detection: 1.5% normal goat serum, 2% bovine serum albumin [BSA] in PBS; IL-1 type 1 receptor detection: 1.5% normal horse serum, 2% BSA in PBS). Tissue sections were incubated in primary antibody overnight at 4°C. For detection of IL-1β, a polyclonal rabbit anti-human antibody diluted 1:750 (Genzyme, Cambridge, MA) was used. For detection of the IL-1 type 1 receptor, a polyclonal goat anti-human antibody diluted 1:750 (R & D Systems, Minneapolis, MN) was used. For each of the antibodies, Western blots were run to confirm the specificity of the antibody in *Xenopus laevis*. Western blot analysis confirmed that the IL-1β antibody recognizes putative frog IL-1β, with molecular weights of 31 kDa and 17 kDa for precursor and mature forms, respectively (Jelaso et al., 1997). We assigned the 17-kDa molecular weight to the active form in the frog, because our recombinant mouse

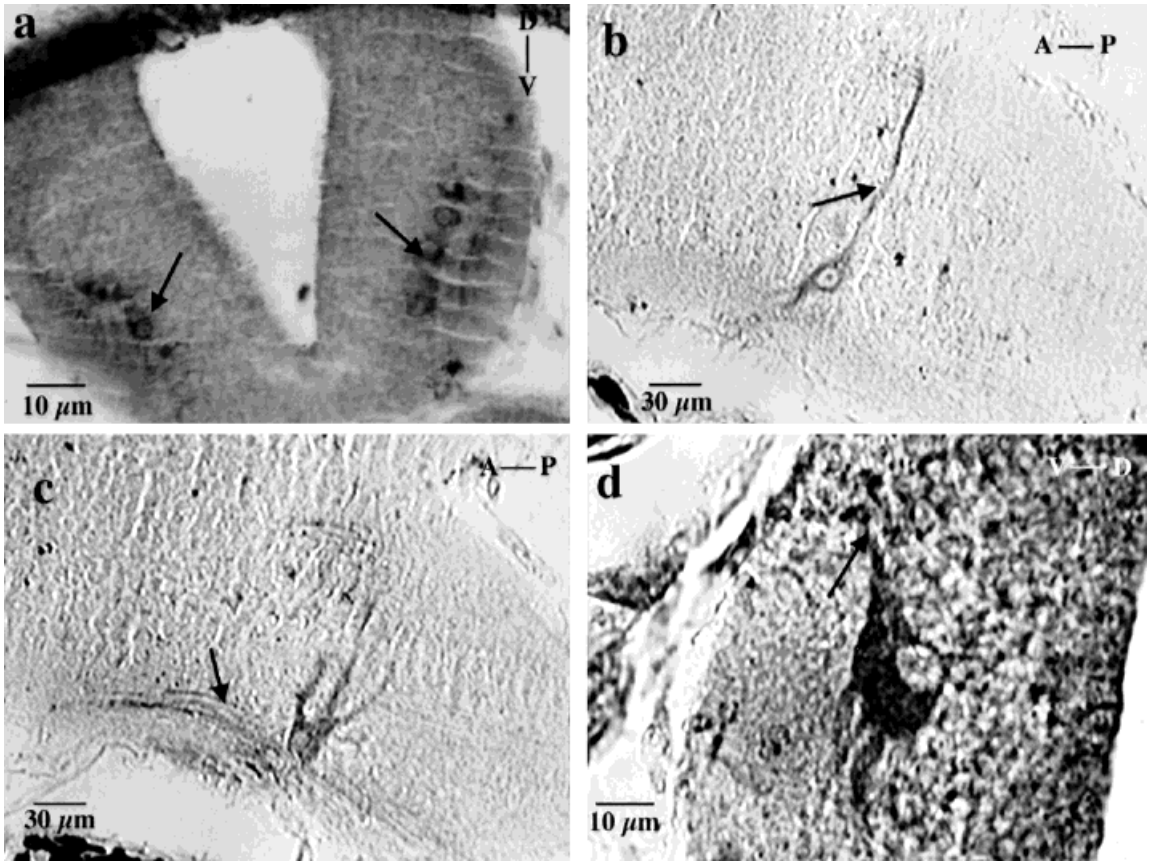

Fig. 2. Interleukin-1 beta (IL-1β) immunoreactivity is observed in specific reticular neurons. **a:** Reticular cells in the midbrain (arrows) of a 4-day-old tadpole. **b:** Mauthner's giant neuron and axon (arrow) are labeled in a 9-day-old tadpole. **c:** Mauthner's neuron and afferents (arrow) are labeled in a 9-day-old tadpole. **d:** The lateral dendrite (arrow) as well as other dendrites are labeled in Mauthner's neuron in a 6-day-old tadpole. D-V, dorsal-ventral orientation; A-P, anterior-posterior orientation.

IL-1β standard (17 kDa) ran at the same position in the gel (19 kDa) as the frog band. The receptor antibody recognized a putative frog protein with a molecular weight of 80.6 kDa (Fig. 1).

Following incubation with primary antibody, the sections were treated for 1 hour with a biotinylated secondary antibody (Vector Laboratories, Burlingame, CA) and then treated with an avidin-horseradish peroxidase (HRP)-biotin complex (Vector Laboratories). Antibody staining was visualized with a 0.05% 3′3′ diaminobenzidine-H_2O_2 (DAB) solution for 10 minutes. The slides were dehydrated through a series of graded alcohols, cleared in xylene, and coverslipped with Permount (Fisher, Pittsburgh, PA). Slides incubated without primary antibody were devoid of staining. For double-label immunocytochemistry, IL-1β was detected with a red alkaline-phosphatase substrate (Vector Red; Vector Laboratories), and the type 1 receptor was detected with a blue peroxidase substrate (TrueBlue; KPL, Gaithersburg, MD).

Immunoreactivity was analyzed by using an Olympus microscope (Tokyo, Japan). The presence of immunoreactivity for a particular cell type or structure was scored in each animal. Figures were made with NIH Image (NIH, Bethesda, MD) and Adobe Photoshop (Adobe Systems, Mountain View, CA) software programs.

Extraction of IL-1 type 1 receptor protein

Thirty 5-day-old tadpoles were collected, anesthetized in tricaine methansulfonate (MS-222), and incubated on ice for 20 minutes in homogenizing buffer (5 mM Tris, 1 mM $MgCl_2$). Tadpoles were homogenized in a Dounce homogenizer. Thirty five milliliters of sucrose solution (0.25 M sucrose, 5 mM Tris-HCl, 1 mM $MgCl_2$) were added to the homogenate followed by centrifugation at 500× g for 5 minutes. The supernatant was collected and centrifuged at 18,000 rpm for 30 minutes in order to separate the membrane fraction. The membrane fraction was resuspended in PBS, and protein concentration was determined with a bicinchoninic acid (BCA) assay (Pierce, Rockford, IL). Membrane-bound receptor proteins were solubilized by incubating the membrane fraction with 8 mM CHAPS for 30 minutes at 4°C followed by centrifugation at 150,000× g for 60 minutes. Protein concentration was determined with a BCA assay.

Gel electrophoresis and Western blot

Proteins were separated by gel electrophoresis by using a Novex (San Diego, CA) Xcell mini-gel apparatus. Membrane protein was mixed with sample buffer (62.5 mM Tris, 2% sodium dodecyl sulfate [SDS], 10% glycerol, 5%

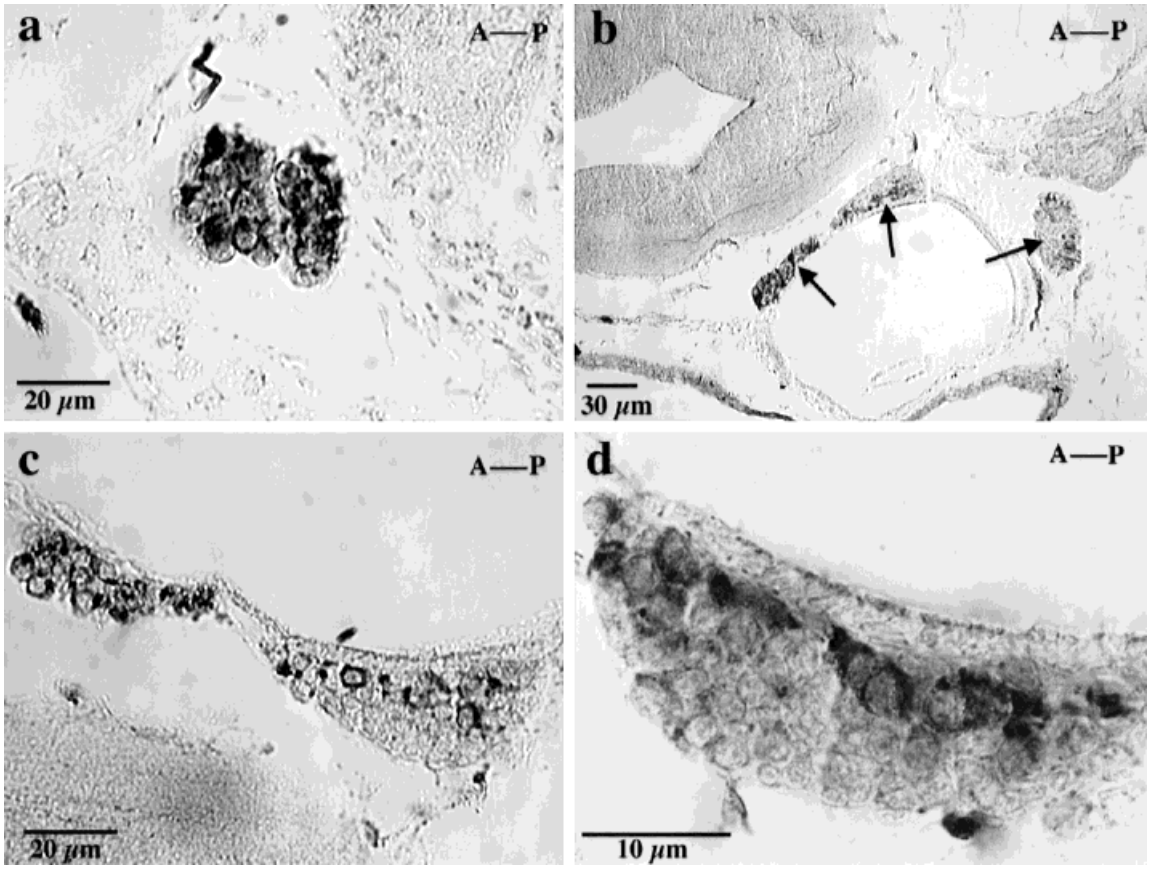

Fig. 3. IL-1β immunoreactivity is observed in the cranial ganglia of a 5-day-old tadpole. **a:** IL-1β protein in the fifth cranial ganglion. **b:** The seventh, eighth, and ninth cranial ganglia (arrows) express IL-1β protein. **c:** The seventh and eighth cranial ganglia at higher magnification (40×). **d:** IL-1β is present in only a specific subpopulation of cells in the eighth cranial ganglion.

β-mercaptoethanol, 0.05% bromophenol blue) and electrophoresed through a 12% Tris-glycine gel. The gel was run at 125 V for 90 minutes and then transferred onto a nitrocellulose membrane (25 V for 90 minutes).

Immunodetection

Antibodies and reagents equivalent to those used on the tissue sections were used on Western blots. The blots were treated with a 5% BSA/0.1% Tween-20 solution overnight at 4°C before incubation for 1 hour with primary antibody diluted 1:100. This was followed by a 1-hour incubation with a biotinylated secondary antibody (1:1,000) and then a 1-hour incubation with an avidin-biotin-alkaline phosphatase (AP) complex (Vector Laboratories). IL-1β immunoreactivity was visualized with the Vector Red alkaline-phosphatase substrate, as described in the immunocytochemistry section above. Blots were scanned into Adobe Photoshop with an Epson ES-1200C scanner. Images were imported into SigmaGel analysis program (Jandel Scientific, San Rafael, CA) for molecular weight determination.

RESULTS

IL-1β and IL-1 type 1 receptor proteins are expressed in specific neural structures in developing *Xenopus laevis*. IL-1β immunoreactivity was observed in neural structures that comprise well-defined locomotor circuits (Table 1; Leghissa, 1941; Stefanelli, 1951) and additional sensory and motor structures (Table 2). Immunoreactivity appeared in most structures as early as day 2 of development and persisted through day 12, the latest developmental stage analyzed.

Early sensory-motor neural structures

Reticular cells. Reticular neurons are involved in controlling early swimming and locomotor behaviors (Kimmel, 1982; Kimmel et al., 1985). Twenty-seven different types of reticular neurons have been identified in the hindbrain and midbrain of zebrafish (Metcalfe et al., 1986). Some reticular neurons receive sensory information from the cranial ganglia and send information to spinal cord motoneurons through descending fiber tracts (Kimmel, 1982; Kimmel et al., 1982; Norlander et al., 1985). Specific reticular neurons in the midbrain (Fig. 2a) and the hindbrain are heavily labeled for IL-1β protein in developing *Xenopus laevis*. Labeling in the midbrain reticular cells is present in 2-day-old tadpoles and begins to attenuate at approximately 7 days, whereas labeling in the hindbrain reticular cells remains constant through day 12 (Table 1).

Mauther's cell circuit. IL-1β immunoreactivity is present in neural structures that comprise the well-defined

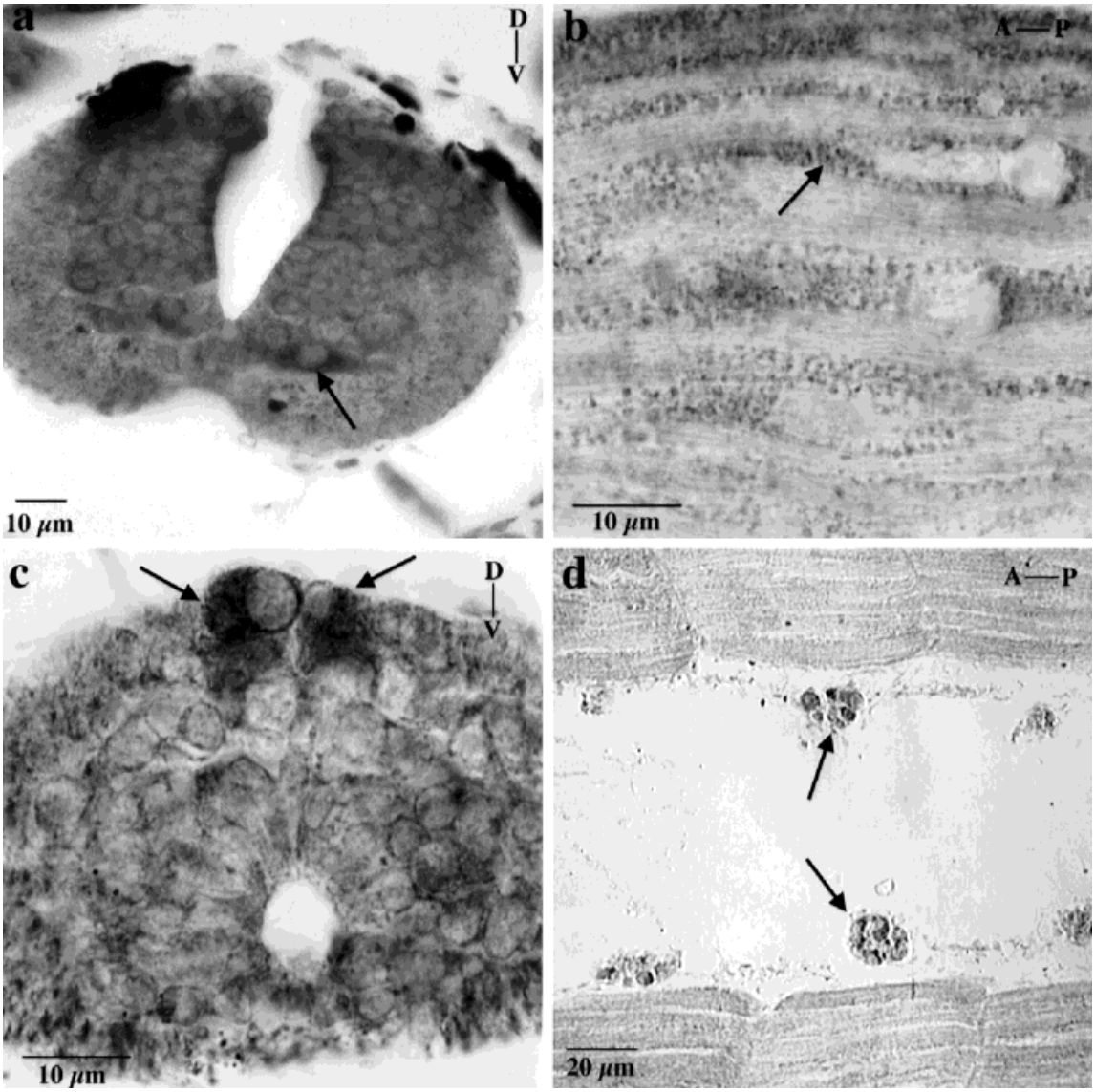

Fig. 4. IL-1β immunoreactivity in the neuromuscular system. **a:** Primary motoneuron (arrow) in a 6-day-old tadpole. **b:** Labeling in the tail musculature (arrow) of a 5-day-old tadpole. **c:** Rohon-Beard neurons (arrows) in a 5-day-old tadpole. **d:** Dorsal root ganglia (arrows) in a 7-day-old tadpole.

locomotor circuit, which controls the startle reflex (Leghissa, 1941; Stefanelli, 1951). The startle reflex is a rapid, unilateral contraction of the tail muscle that is elicited in response to vestibular, lateral line, and/or tactile sensory stimuli (Eaton and Bombadieri, 1978; Kimmel, 1982). Mauthner's neuron is a giant, bilateral, reticular neuron in the hindbrain that plays an integral role in mediating the startle reflex (Fig. 2b–d; Zottoli, 1977; Eaton et al., 1988). Mauthner's neuron receives sensory information from the trigeminal (fifth), lateral line (seventh), and vestibular (eighth) cranial ganglia (Fig. 3) and synapses with primary motoneurons (Fig. 4a) in the contralateral spinal cord that synapse with trunk musculature (Fig. 4b; Bartelmez, 1915; Kimmel et al., 1981; Metcalfe et al., 1985; Kimmel and Westerfield, 1988). The fifth, seventh, and eighth cranial ganglia, Mauthner's neuron, primary motoneurons, and tail musculature all show IL-1β immunoreactivity from day 2 of development.

Trunk sensory system. Rohon-Beard neurons (Fig. 4c) are primordial sensory neurons in the spinal cord that are replaced by dorsal root ganglia (Fig. 4d) later in development (Hughes, 1957; Lamborghini, 1980, 1987; Kimmel and Westerfield, 1988). They are large, identifiable neurons that synapse with the skin and tail muscle and send ascending fibers into the lateral longitudinal fasiculus (llf; Norlander et al., 1985). Rohon-Beard neurons are the main sensory element of the trunk involved in controlling early locomotor behavior (Eaton and Farley, 1973; Clarke et al., 1984; Soffe et al., 1984). IL-1β immunoreactivity is present in the Rohon-Beard neurons from 2 days onward. The dorsal root ganglia begin to appear at 3 days and are labeled from the time they emerge.

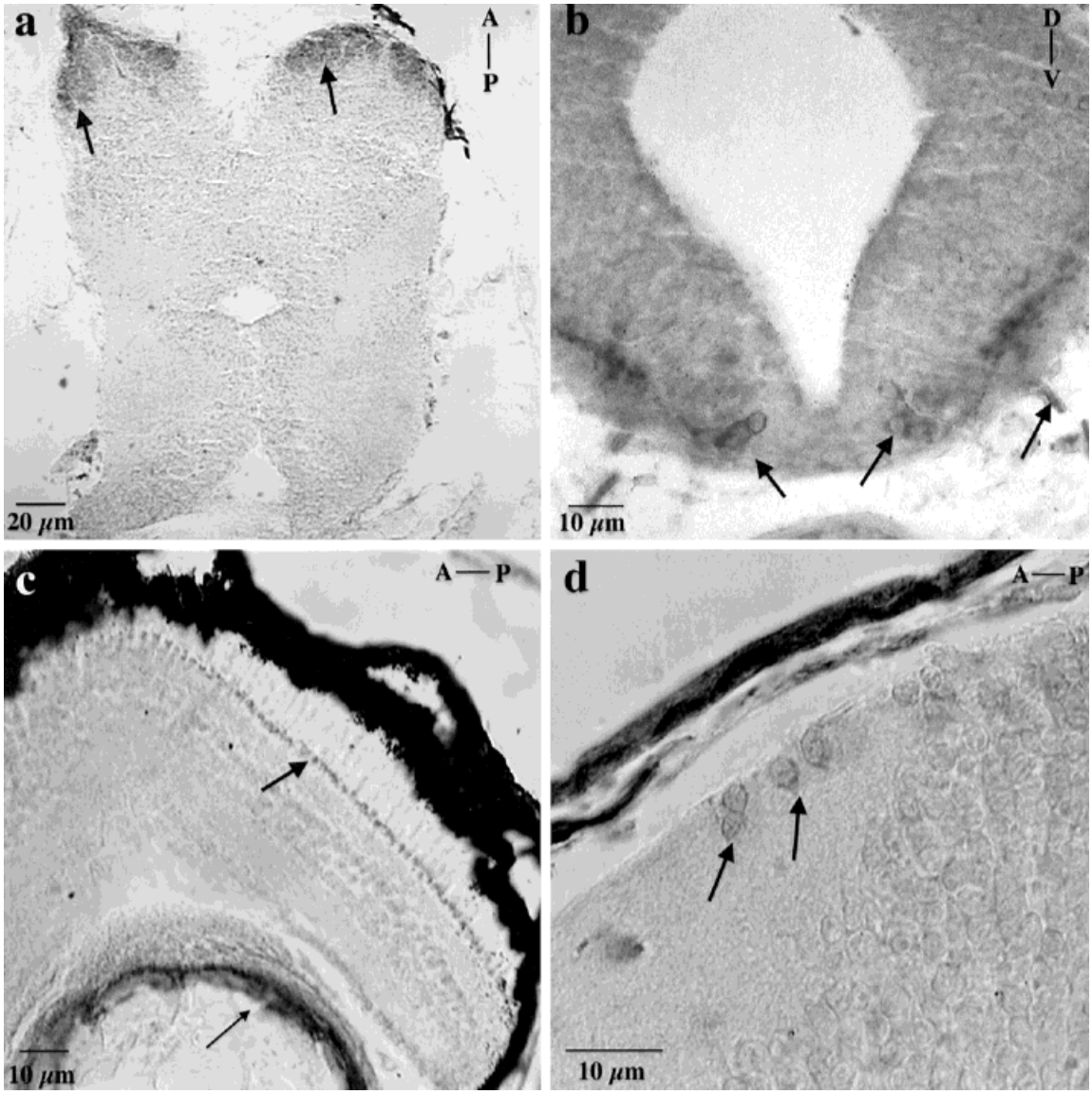

Fig. 5. IL-1β immunoreactivity in additional sensory and motor structures of the developing frog. **a:** IL-1β immunoreactivity in the olfactory bulbs (arrows) of a 5-day-old tadpole. **b:** IL-1β in the oculomotor nerve and associated neurons (arrows) in the brain of a 4-day-old tadpole. **c:** IL-1β in the retina (thick arrow points to photoreceptors) and outer growth zone of the lens (thin arrow). **d:** IL-1β in the lateral Purkinje cells of the cerebellar auricle (arrows).

TABLE 3. IL-1 Type 1 Receptor Immunoreactivity in Sensory and Motor Structures That Comprise Locomotor Circuits[1]

Age (days)	Total animals (n)	Cranial ganglia			Reticular cells			Tail structures		
		Fifth	Seventh	Eighth	Mauthner's	Hindbrain	Midbrain	RB/MN	DRG	Muscle
2	12	100	100	100	0	100	84	92	0	100
5	10	100	90	90	70	90	80	90	60	100
8	8	100	100	100	100	100	100	100	88	100
12	7	100	100	100	88	100	100	86	71	100

[1]Total numbers of animals analyzed per day of development are listed above. Animals were scored for the presence of IL-1β immunoreactivity, which is represented as a percentage of the total number of animals scored for that day of development. For abbreviations, see Table 1.

Other structures. Additional sensory and motor structures express IL-1β during tadpole development. The olfactory pit, nerve, and bulb are labeled (Fig. 5a) as well as the oculomotor (Fig. 5b) and optic nerves. IL-1β immunoreactivity is present in retinal cells and appears darkest in photoreceptor inner segments (Fig. 5c). The outer growth zone of the lens (Fig. 5c), the (primordial) Purkinje cells of the lateral cerebellar auricle (Fig. 5d), and diffusely distributed cells in the hypothalamus also express IL-1β protein.

TABLE 4. IL-1 Type 1 Receptor Immunoreactivity in Other Neural Structures[1]

Age (days)	N	Cranial nerves I	Cranial nerves II	Retina	Optic and cranial muscles	Hypothalamus	Cerebellum
2	12	100	100	92	100	92	58
5	10	90	100	100	100	100	80
8	8	75	100	100	100	88	100
12	7	71	100	100	100	86	71

[1]Total numbers of animals analyzed per day of development are listed above. Animals were scored for the presence of IL-1β immunoreactivity, which is represented as a percentage of the total number of animals scored for that day of development.

IL-1 type 1 receptor protein

Comparison of Tables 3 and 4 with Tables 1 and 2 shows that the IL-1 type 1 receptor protein is always colocalized with IL-1β in specific neural cells in the developing frog (Fig. 6). IL-1 type 1 receptor immunoreactivity appears in the vicinity of the cell membrane and in the nucleus, as seen in Mauthner's neuron (Fig 6b). Neural cell types that do not express IL-1β also do not express the IL-1 type 1 receptor. The only cells within the nervous system that were found to express the receptor independent of the presence of IL-1β were fibroblast-type cells external to the cranial ganglia (Fig. 6c).

DISCUSSION

The cytokine IL-1 plays an important role in regulating the immune system, initiating a wide range of immune responses, which include costimulation of thymocyte proliferation, enhancement of B-cell proliferation and differentiation, production of fever, production of acute-phase proteins by hepatocytes, induction of neutrophilia, and stimulation of prostaglandin and collagenase from synovial cells (Dinarello, 1991). IL-1 is evolutionarily conserved and has been identified in several species of mammals, birds, fish, and invertebrates (Siegel et al., 1986; Beck et al., 1989; Hughes et al., 1990; Cohen and Haynes, 1991). Watkins et al. (1987) identified a molecule with IL-1-like activity in peritoneal cells of the frog *Xenopus laevis*. We have recently demonstrated that a polyclonal antibody directed against human recombinant IL-1β recognizes putative frog IL-1β proteins with molecular weights of 17 kDa and 31 kDa (Jelaso et al., 1997). In this paper, we demonstrate that *Xenopus laevis* also expresses a putative IL-1 type 1 receptor protein with a molecular weight of 80.6 kDa, similar to the 80-kDa mammalian protein. IL-1β and the IL-1 type 1 receptor proteins are coexpressed in a distinct pattern in the developing nervous system of *Xenopus laevis*, suggesting that IL-1β may play an important role in neural development in addition to its role in the immune system. Colocalization of IL-1β and its type 1 receptor in individual cells suggests that IL-1β may elicit its effects through an autoregulatory mechanism. The presence of IL-1β and the IL-1 type 1 receptor in the nucleus of, for example, Mauthner's neuron, is consistent with reports that the IL-1β-receptor complex can be translocated to the nucleus of the EL-4 T-cell line (Curtis et al., 1990). In the immune system, IL-1 can induce its own gene transcription (Dinarello et al., 1987; Warner et al., 1987).

Although the role of IL-1β in regulating neural-immune interactions in the damaged nervous system is well established (Giulian et al., 1988a; Merrill, 1992; Rothwell and Strijbos, 1995; Scripter et al., 1997), its role in neural development is not yet understood. There is some evidence that other immune system cytokines can play a trophic role in the developing nervous system (Hama et al., 1989; Martinou et al., 1990; Neff et al., 1993; Oppenheim et al.,

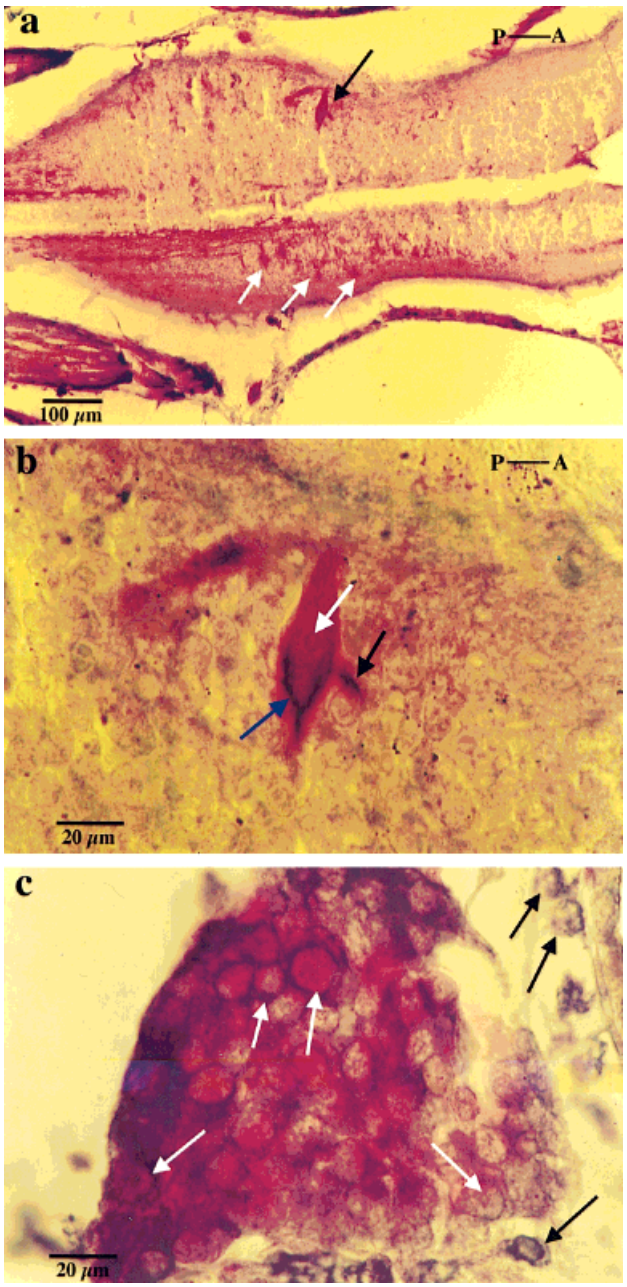

Fig. 6. Expression of IL-1β and the IL-1 type 1 receptor in developing *Xenopus laevis*. **a:** Hindbrain reticular neurons (white arrows), including Mauthner's neuron (black arrow), show IL-1β immunoreactivity (red) and IL-1 type 1 receptor immunoreactivity (blue). **b:** Higher power view (100×) of Mauthner's neuron. Note expression of IL-1 type 1 receptor (blue) in the nucleus (white arrow), ventral dendrite (black arrow), and axon hillock (blue arrow). **c:** Cells of the ninth cranial ganglion are both double labeled (white arrows) for IL-1β (red) and its type 1 receptor (blue). Surrounding fibroblast-type cells are single labeled for the IL-1 type 1 receptor (blue label, black arrows).

1993; Tabira et al., 1995). IL-1 can increase survival of developing spinal cord neurons in the mouse (Brenneman et al., 1992, 1995). On the other hand, there is evidence that IL-1β may play a role in apoptosis in the developing nervous system. Jarskog et al. (1997) have recently shown that IL-1β can decrease survival of dopaminergic neurons in the substantia nigra of embryonic mice. In addition, IL-1β is linked with apoptosis via its association with the interleukin-converting enzyme (ICE). ICE cleaves pro-IL-1β into its active form (Black et al., 1988). ICE, which is also referred to as caspase 1 (Alnemri et al., 1996), is the mammalian homolog of ced-3, the death-initiating gene in *C. elegans* (Ellis and Horvitz, 1986; Yuan et al., 1993; Wilson et al., 1994; Nicholson et al., 1995). ICE can induce apoptosis in several systems (Thornberry et al., 1992; Miura et al., 1993; Alnemri et al., 1995), and ICE inhibitors can block apoptosis (Ray et al., 1992; Gagliardini et al., 1994; Milligan et al., 1995).

There are many possibilities regarding the role of IL-1β in the developing nervous system of the frog. One is that IL-1β, acting as a trophic factor, may influence growth and/or survival of neurons. The expression of IL-1β protein in cells that are long-lived, such as Mauthner's neuron, supports this hypothesis. IL-1β may influence survival by inducing expression of other cytokines or growth factors. IL-1 can induce expression of NGF protein in glial cells of the adult rat (Lindhom et al., 1987; Gadient et al., 1990) as well as LIF (Aloisi et al., 1994) and IL-6 (Benveniste et al., 1992). In addition, IL-1β mRNA is colocalized with NGF mRNA in cells in the central nervous system of the adult rat (Bandtlow et al., 1990).

The presence of IL-1β and its type 1 receptor in the anterior forebrain structures and cells, such as the hypothalamus, suggests that IL-1β may be involved in the developing neuroimmunoendocrine system. The role of IL-1β in mediating hypothalamopituitary-adrenal (HPA) axis function is well established (Besedovsky et al., 1991; Matta et al., 1993; Ericsson et al., 1994).

Another possibility is that IL-1β, like other neurotrophins, may play a role in the formation or maintenance of functional neural circuits (Patterson, 1993; Katz and Shatz, 1996). BDNF and NT-3 promote functional maturation and efficacy of neuromuscular synapses in the frog *Xenopus laevis* (Wang et al., 1995; Stoop and Poo, 1996), and BDNF and its receptor, *trkB*, are involved in *Xenopus* visual system development (Cohen-Cory et al., 1996). IL-1β and its type 1 receptor may influence maturation of neural structures that comprise the earliest functional behavioral circuits in the developing *Xenopus* nervous system.

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