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COMMENTARY

Molecular Mechanisms of Fyn-Tyrosine Kinase for Regulating Mammalian Behaviors and Ethanol Sensitivity

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ABSTRACT. Mice lacking Fyn, a Src-related non-receptor tyrosine kinase, show impairment of various behaviors, such as spatial learning, suckling, emotional behaviors, and ethanol sensitivity. These mice also display both morphological defects and impairment of synaptic function. Fyn is highly expressed in the mammalian CNS from embryonic day 8.5 to adulthood. Pharmacological and electrophysiological analyses of mice lacking Fyn reveal γ-aminobutyric acid and glutamatergic defects. We propose here the hypothesis that these defects are caused separately by developmental disorganization and impairment of synapse function by a deficit in Fyn. Regarding the glutamatergic defect, in particular, after ethanol administration the *N*-methyl-D-aspartate (NMDA)-dependent function is recovered by Fyn, paralleled with tyrosine phosphorylation of NMDA receptor 2B subtype. Thus, modulation of the NMDA receptor function by Fyn may have a significant role in building and regulating sophisticated neural circuits and behavior. In addition, the cadherin-related neural receptor (CNR) family is isolated by binding activity for Fyn. The CNR–Fyn complex will also open a new angle for gaining insight into the molecular mechanisms for regulating mammalian behavior. BIOCHEM PHARMACOL **57**;8:845–850, 1999. © 1999 Elsevier Science Inc.

KEY WORDS. emotion; learning; suckling; synapse; cadherin; Fyn kinase to regulate behaviors

Developing gene conversion techniques in mice opens the field for analyzing the molecular mechanisms regulating mammalian behavior. This behavior is generated basically from numerous complex neural networks in the brain. To understand mammalian behavior, we need to gain insight into the molecular mechanisms that produce the enormous numbers of cell–cell interactions in mammalian brain that yield highly organized patterns. Protein tyrosine kinases are candidates for involvement in signaling pathways that regulate cell–cell interactions. It is known that these pathways control cellular proliferation, differentiation, and function in a variety of cell types. Fyn, which belongs to the Src family of tyrosine kinases, is expressed extensively in the mammalian brain [1]. In neurons, Fyn is concentrated in nerve growth cone membranes [2, 3] and in the PSD† fraction [4]. Loss of function in mice is related to several behavioral defects in the CNS, such as spatial learning, as tested in the Morris water maze [4], suckling behavior [5], hyper-responsiveness to fear-inducing stimuli [6], enhanced susceptibility to audiogenic seizures [7], and hypersensitivity to ethanol [8]. These defects suggest that Fyn plays a critical role in determining mammalian behaviors. However, there is a huge black box between Fyn and several behaviors. Here, recent works seeking to understand this black box (summary in Fig. 1) are introduced.

Fyn EXPRESSION IN THE MAMMALIAN BRAIN

Fyn expression in neural tissues appears to be developmentally regulated [10, 11]. The findings were: (1) Fyn was first detected in the luminal surface of the neuroectoderm along the entire neural groove at embryonic day 8.5; (2) the expression was increased during differentiation and migration of neuronal cells; (3) the expression in the neuronal cells was intense in the development of neural fibers; (4) high expression was found, in particular, in olfactory and optic tracts in the late embryonic stage; (5) the expression in the cranial nervous system increased until pups were born; (6) the expression level gradually decreased after birth; (7) after birth, the expression increased in neural fiber tracts, which were being myelinated by the oligodendrocytes, and also in the oligodendrocytes; (8) from young to adult, intense expression was found in the olfactory bulb, piriform cortex, amygdaloid body, hippocampus, cerebral

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† *Abbreviations:* CNR, cadherin-related neural receptor; EC, extracellular cadherin; EPSP, excitatory postsynaptic potential; GABA, γ-aminobutyric acid; LORR, loss of righting reflex; LTP, long-term potentiation; NCAM, neural cell adhesion molecule; NMDA, *N*-methyl-D-aspartate; NMDAR, NMDA receptor; NR2A, NMDA receptor 2A subtype; NR2B, NMDA receptor 2B subtype; PSD, postsynaptic density; and QTL, quantitative trait locus.

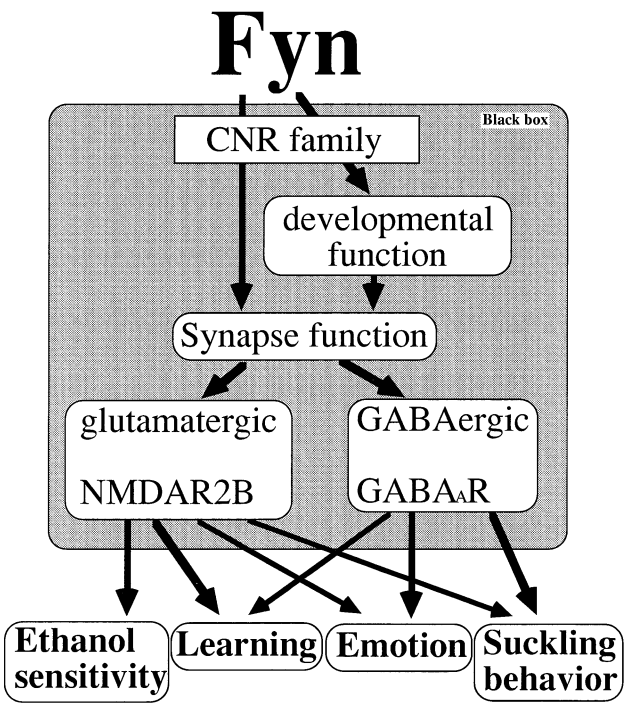

FIG. 1. A black box between Fyn tyrosine kinase and several behaviors. Mice lacking Fyn display hypersensitivity to ethanol, impaired spatial learning, modulation of emotional behavior, and a defect of suckling behavior. In the black box, Fyn-minus mice also display defects of developmental and synaptic functions. These defects may induce the impairments of glutamatergic and GABAergic function. We recently found a novel CNR (cadherin-related receptor) family by studying Fyn-binding activity in mouse brain [9]. This family may contribute to synapse and developmental functions, together with Fyn.

cortex, thalamus, and cerebellum; and (9) at the adult stage, the expression was characteristic in the sensory pathway, the dorsal horn of the spinal cord and sensory nuclei such as ventral and dorsal cochear nuclei, inferior colliculus, and medial geniculate nucleus in the auditory pathways [1]. These observations indicated that Fyn expression parallels neural tube formation, neural cell migration and differentiation, extension of the processes, myelination, synaptogenesis, the sensory pathway, and information processing from input.

LEARNING DEFECTS OF Fyn-DEFICIENT MICE

Fyn-deficient mutation caused impaired Schaffer collateral LTP and spatial learning of the Morris water maze [4]. *Fyn*-knockout mice also appeared to have undulating cell layers of CA3 and dentate gyrus regions [4, 10]. In Fyn-rescue mice that expressed a fyn cDNA only in neurons of the adult forebrain, Schaffer collateral LTP was restored, even though the morphological abnormalities characteristic of Fyn-deficient mice were still present [12]. LTP is thought to support learning and memory and requires the NMDA receptor-dependent influx of Ca^{2+}. The Src family kinase protein-tyrosine phosphorylation is stimulated by NMDA receptor activation [13], and inhibitors of the Src family kinases can block the induction of LTP [14]. Indeed, the NR2A and 2B subunits of the NMDA receptor are the targets of tyrosine phosphorylation by Fyn *in vitro* [15]. After LTP induction, the tyrosine phosphorylation of NMDA receptor 2B is increased [16, 17]. However, the hypothesis that Fyn targets the NMDA receptor 2B during LTP formation has not been confirmed.

Fyn-knockout mice are impaired at spatial learning in a water maze [4]; however, after their hind feet were mechanically stimulated, this deficit could be largely overcome [18]. Thus, Fyn-deficient mice may have a movement impairment that results from motor, sensory, or motivational factors. In another spatial learning, radial maze task, Fyn-deficient mice showed no impairment when food was used as a reward [19]. These results indicate that Fyn mice normally have the ability of spatial learning. The deficits in water maze learning may be attributable to the increased reactivity to the aversive or stressful nature of this task rather than to deficiencies in spatial learning itself. Indeed, Fyn-deficient mice have several emotional defects, as described below. Thus, it is necessary to further confirm the spatial learning defects of Fyn-deficient mice.

IMPAIRED SUCKLING BEHAVIOR

Fyn-deficient pups derived from a cross between Fyn-deficient parents usually died within 2 days after birth. Litters containing only Fyn-deficient pups were hardly nursed by their Fyn-deficient mothers. Addition of a wild-type pup rescued these pups from death. Thus, the death of the pups was caused not only by their lack of Fyn, but also by the Fyn-deficient mothers. In Fyn-deficient pups, the capability of finding their mother's prelactated nipples was reduced [5]. However, the death phenotype was influenced by the feeding environment [1]. This phenotype was observed in autoclaved Douglas fir chips, but not in chips that were not autoclaved. Gas chromatography analysis revealed that several new odors emerged from the autoclaved chips. Fyn-deficient females avoided the odors and hardly nursed the Fyn-deficient pups in the presence of these odors (unpublished data). Thus, the stressful odors may block the maternal behavior of Fyn-deficient mothers. The hypersensitivity of the Fyn-deficient mother to the stressful odors may arise from an abnormality of the olfactory pathway for recognizing the odors. Actually, there is a reduced sensitivity to antagonists of $GABA_A$ receptors and impaired NMDA receptor-dependent LTP in the olfactory bulb of Fyn-deficient mice [20]. Olfactory information is processed by GABAergic and glutamatergic synapses in the olfactory neurons [21, 22]. Therefore, impairments in the $GABA_A$ and NMDA receptors of Fyn-deficient mice may cause the defect in odor recognition in the maternal behavior.

IMPAIRMENTS IN EMOTIONAL BEHAVIORS

Like the suckling phenotype, the response patterns to several environmental stresses in Fyn-deficient mice were

altered. Since emotionality is based on these response patterns, Fyn-deficient mice have emotional abnormalities. Homozygous *Fyn*-mutant mice exhibited stronger light aversion in a light–dark choice test and higher fear–response scores in the novelty preference, the passive avoidance, and the elevated plus maze tests than did heterozygous mice [6, 7]. These results indicated that mice lacking Fyn are hyper-responsive to fear-inducing stimuli. These emotional defects are induced by a lesion of the amygdaloid body where Fyn is expressed extensively. Fyn-deficient mice have an electrophysiological defect in the amygdaloid body on kindling [23]. Maternal behavior is also based in the amygdaloid body [24].

To further confirm the emotional abnormalities of Fyn-deficient mice, we measured the modulation of seizure susceptibility. A positive correlation has been reported in the relationship of timidity (fearfulness) to audiogenic seizure susceptibility. Actually, the susceptibility to acoustically primed audiogenic seizure is enhanced in Fyn-deficient mice [7]. We also examined the susceptibility to seizure induced by drugs in the Fyn-deficient mice. Fyn-deficient mice were significantly more likely to show myoclonic convulsions than were heterozygote mice when kainic acid, NMDA, pentylenetetrazol, picrotoxin, and bicucullin were administered. On the other hand, no difference in seizure susceptibility was found when strychnine was administered. These findings provide the evidence of abnormal function in the GABAergic and glutamatergic synapses of Fyn-deficient mice [25]. Modulation of emotional behavior in Fyn-deficient mice may be based on defects of the GABAergic and glutamatergic synapse function. Evidence of kindling defects in the amygdaloid body of Fyn-deficient mice also supports the emotional abnormalities.

ETHANOL SENSITIVITY OF Fyn-DEFICIENT MICE

Ethanol is among the most widely abused drugs in the world. Genetic components affect the determination of the behavior responses to ethanol by QTL and gene targeting analyses; however, the neural mechanisms responsible for it causing intoxication and dependence are largely unknown. Ethanol modulates the function of NMDA and $GABA_A$ receptors, which have phosphorylated tyrosine residues. Fyn-deficient mice have learning and emotional defects, like the DBA/2 mouse strain. DBA/2 mice also have a hypersensitivity to ethanol [26]. Using this analogy, we assessed the hypnotic effect of ethanol sensitivity of Fyn-deficient mice. The duration of the LORR after ethanol administration was markedly longer in Fyn-deficient mice than in control mice. However, no significant differences were found in the duration of the LORR after flurazepam (a benzodiazepine derivative) administration. The degradation curve of the ethanol in the blood showed no significant differences between Fyn-minus and control mice. Thus, lack of Fyn enhanced the sensitivity to ethanol in their CNS. To understand the effect of Fyn in the brain, we measured the level of tyrosine phosphorylation in the various brain regions after ethanol administration to Fyn-minus and control mice. In the control (wild-type) hippocampus, there was a significant enhancement in tyrosine phosphorylation of NMDA receptor 2B subtype 5 min after ethanol administration, whereas in Fyn-deficient mice there was no enhancement. The lack of this up-regulation in Fyn-deficient mice indicates that it is mediated mainly by Fyn. Thus, in the hippocampus, Fyn can phosphorylate tyrosine residues of the NR2B receptor depending on ethanol administration. It is known that ethanol inhibits NMDAR-mediated EPSPs in hippocampal slices (acute tolerance) [27]. This acute tolerance was found in the hippocampal slices of control mice but not of Fyn-deficient mice. An enhanced time course of tyrosine phosphorylation of NR2B after ethanol treatment in Fyn-plus mice suggested that the acute tolerance to ethanol was induced by NR2B phosphorylation of Fyn. Furthermore, the acute tolerance was eliminated when ethanol was administered with ifenprodil, an agent considered to be a selective antagonist of NMDAR containing NR2B [28]. Thus, modulation of NMDAR function by Fyn seems to be involved in the development of acute tolerance to ethanol.

MOLECULAR FUNCTION OF Fyn AT THE SYNAPSE

Several behavioral defects (learning, suckling, emotion, and ethanol sensitivity) in Fyn-deficient mice are derived in large part from synaptic dysfunction. In particular, NMDA and $GABA_A$ receptors are modulated in mice lacking Fyn. At the site of the NMDA receptor, Fyn is most important for phosphorylation of the NR2B subtype. On the other hand, the modulation of $GABA_A$ receptors by Fyn is unclear. However, Fyn-deficient mice display disorganized architecture of the neuron layer in the hippocampus; also, Fyn is expressed during developmental stages such as neuronal cell migration and differentiation, axon guidance, target recognition, and synaptogenesis [1]. We, therefore, propose the hypothesis that Fyn plays an important part in building the neural circuits of the GABAergic neurons. For building the neural circuits, cell–cell interaction is a key function. Recent works support the theory that Fyn connects to a novel cell–cell function for building the neural circuits.

Fyn is localized under the cellular plasma membrane and participates in transducing the extracellular signal into the cytoplasm. In several tissues, Fyn is associated with diverse receptor proteins, such as the CD3 component of the T cell receptor complex in T cells [29], and the membrane binding IgM complex in B cells [30]. In the nervous system, Fyn is bound to myelin-associated glycoprotein, a myelin-specific glycoprotein in oligodendrocytes during early myelin formation [31]. The nicotinic acetylcholine receptor, which mediates depolarization at the neuro-muscular junction, has been shown to bind to Fyn in the *Torpedo* electric organ [32]. Fyn also binds to the neural cell adhesion molecule 140 (NCAM140) isoform, which is found in

migrating growth cones [33]. It is colocalized with NCAM on many axonal tracts in the developing central and peripheral nervous systems and in the olfactory system [3, 34] and mediates NCAM-dependent neurite growth [35]. However, since the CNS is a diverse and complex system, little is known of how receptors are coupled with Fyn, particularly in the mammalian synapse. We hypothesize that Fyn is coupled with a family of proteins found in multiple types of receptors during synapse formation, and that the molecular diversity of these proteins imparts specific cell surface properties to neurons or synapses, one of which may be differential cell–cell recognition.

While searching for proteins that directly interact with Fyn in a yeast two-hybrid system [36], we identified new cadherin-like genes, named the cadherin-related neuronal receptor (CNR) family [9]. This new cadherin subfamily exhibits homology with the classical cadherins in the extracellular domain but is quite different in the intracellular domain. The extracellular domain is composed of six cadherin repeats (unlike the five of the classical cadherins) and an additional RGD motif, the consensus integrin binding sequence, contained within the first cadherin repeat, EC1. The intracellular domain contains several PXXP motifs of binding consensus to the SH3 domain. Fyn can associate with the intracellular domain. The CNR family consists of as many as 20 individual genes that are widely found in brain regions and cell types. Immunoglobulin, T cell receptor, and olfactory receptor [37] genes generate immunological and neurological diversity. Diverse odorant receptors binding to different odor molecules function as axonal guidance receptors for finding the appropriate target [38]. Thus, diversity among homologous receptor molecules may be involved in specified or selective cell–cell recognition. CNR family members may fulfill these features in CNS neurons, and, therefore, the diversity of the CNR family might induce differential cell differentiation, cell migration, synaptic connections, or neural networks in the mammalian CNS. *In situ* hybridization analyses revealed that CNR family members are differentially expressed in the individual neurons, even in the same brain region. This CNR family is restricted to a portion of neurons of the same type. On the other hand, cadherins are locally expressed, particularly in developing brain nuclei, fiber tract, and neural circuits, but as a whole are expressed in the same types of neurons [39, 40]. The expression of the mRNAs in the brain was present from embryonic day 15, was highest at postnatal day 10, and was reduced at the adult stage. Therefore, CNRs are likely to play a significant role in neuronal migration, axon guidance, target recognition, and synaptogenesis. Supportive of this assertion is the observation that mice lacking Fyn, and presumably lacking in CNR-mediated cellular regulation that is dependent on Fyn, display morphological defects in the neuronal architecture of the hippocampus [4, 10] and decreased neurite outgrowth [12]. Lack of the CNR-mediated signal transduction of Fyn may disorganize the neural circuits in several brain regions.

In the adult brain, CNR protein is concentrated in the PSD fraction and localized in the synaptic junction. The PSD, which is comprised of submembranous cytoskeletal elements of the postsynaptic structure of synapses, contains adhesion molecules between pre- and postsynaptic membranes, neurotransmitter receptors, and several signal transduction proteins, such as Fyn. Mice in which PSD proteins are disrupted show impairment of LTP and abnormalities in learning and in several other behaviors, indicating that the proteins present in the PSD fraction are critical to synaptic plasticity. Since CNR family members include motifs involved in both cell adhesion and signal transduction, they are candidate molecules relevant to synaptic connectivity and plasticity. Fyn-minus mice are impaired in LTP induction in the hippocampus [4] and olfactory bulb [20], and have defects in spatial learning in the Morris water maze and response to stressful odors. The mechanisms contributing to synaptic forms of plasticity are still a topic of intense debate. One proposed hypothesis is that specific patterns of activity could lead to modifications of synaptic structure. Another proposed hypothesis is that specific patterns of activity could lead to modifications of synaptic structures and, eventually, to changes in synaptic connectivity. In line with the hypothesis of structural reorganization at the synapse, it is reported that NCAM, L1, and cadherins contribute to synaptic plasticity [41–44]. The members of the CNR family are also candidates in line with this hypothesis. Since tyrosine phosphorylation of NR2B is increased after LTP induction [16, 17], it is possible that LTP induction increases Fyn activity, which could, in turn, regulate synaptic strength by acting on the CNRs, perhaps causing changes in activation of NMDA receptor function and in synaptic structure critical to the expression of LTP.

CONCLUSION

Fyn signal transduction in neurons is essential to build neural circuits during development, to regulate learning, suckling, and emotional behaviors, and to determine sensitivity to ethanol. Mice lacking Fyn show various behavioral phenotypes; pharmacological and electrophysiological evidence suggests that these abnormalities are based on the GABAergic neuronal defects and on the reduction of the NMDA receptor function, depending on the NR2B phosphorylation at the synapse. To understand the mechanisms for ethanol-induced intoxication and learning, we should confirm the tyrosine phosphorylation sites of NR2B by Fyn after ethanol administration and LTP induction and produce a specific antibody for the sites. Staining may be able to confirm the specific neural circuits during intoxication and learning. Downstream of the Fyn-signaling pathway are Fak [45], Wiskott-Aldrich Syndrome protein (WASP) [46], hnRNP K [47], mDab1 [48], TH82, TH34 [36], and p130,*

* Yasuda M and Yagi T, Identification of p130, a brain-specific Fyn-associated protein that has a subtype in DBA/2 mice. Abstract, 27th Annual Meeting of the Society for Neuroscience, Vol. 23, p. 1466, 1997.

which are likely to play a part in the modulation of the cytoskeleton and/or alteration of protein synthesis for building the neural circuits. Upstream of Fyn, the CNR family, which contains cell adhesion structures, may control the Fyn signal pathway in neurons for building the neural circuits. The CNR–Fyn pathway will open up new angles to approach many aspects of behavioral regulation and drug sensitivity. On the other hand, to separate several problems of Fyn mutants, such as GABAergic or glutamatergic, developmental, or synaptic defects, and learning or emotion, we should perform conditional targeting of Fyn.

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