ISSN 0253-9756 Acta Pharmacologica Sinica 中国药理学报 1999 Jan; 20 (1): 3 - 9
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Review

High-voltage-activated calcium current and its modulation by dopamine D_4 and pituitary adenylate cyclase activating polypeptide receptors in cerebellar granule cells

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KEY WORDS cerebellum; dopamine receptors; PACAP receptors; calcium channels; electrophysiology

ABSTRACT Cerebellar granule cells were a good mold for electrophysiologic studies at the single neuron level. Two distinct types of high-voltage-activated Ca^{2+} channels were present in cerebellar granule cells. These calcium channels change their expression, gating, and pharmacological properties during development, suggesting that calcium channel must be related to the processes of granule cell maturation and excitability. Dopamine inhibited L-type calcium current by activating D_4 receptor, and this effect might involve another signaling system with the exception of cAMP system. The functional D_4 receptor discovered in cerebellum not only gave a possibility to find other antipsychotics, but also supported the existence of a dopaminergic system in the granule cell involving the D_4 receptor. Pituitary adenylate cyclase activating polypeptide (PACAP) could increase intracellular Ca^{2+} content by activation of Ca^{2+} channel and mobilization of intracellular Ca^{2+} stores. The effects were also cAMP-independent. Activating Ca^{2+} currents might be an important and necessary role of PACAP as a neurotropic factor involved in the control of multiplication, differentiation, and migration of granule cells.

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Received 1998-04-17 Accepted 1998-09-25

The electrophysiologic study of isolated single central neurons from mammals was hampered by the difficulty in obtaining a homogeneous cell population. Cerebellar granule cells were the most abundant neuron types in the mammalian central nervous system. Primary cultures of cerebellar neurons from postnatal 8-d rat contain >95 % granule cells, and cells of different types were very infrequent and easily identified by their morphology[1]. Therefore, this preparation was particularly suitable for studies at the single cell level. However, the granule cells were too small (only 5 - 8 μm diameter) to be studied with conventional microelectrodes and only the advent of the patch-clamp technique has made it possible to study their electric properties and voltage-dependent currents[2,3]. In addition, some excitatory and inhibitory amino acid receptors such as non-NMDA glutamate receptor, NMDA receptor, and GABA receptor had been discovered. The currents evoked by these released neurotransmitters from Geology cell and mossy fiber terminals had been investigated[4,5].

Voltage-gated Ca^{2+} channels were very important because of the unique role of Ca^{2+} in a variety of neuronal functions: besides carrying a depolarizing current which could sustain the action potential, it modulated neurotransmitter release and activated enzyme system and other ionic channels directly[6]. Here presented a patch-clamp study of Ca^{2+} currents in neonatal rat cerebellar granule cell and some new recep-

ISSN 0253-9756 Acta Pharmacologica Sinica 中国药理学报 1999 Jan; 20 (1)
E-mail aps@server.shcnc.ac.cn Phn/Fax 86-21-6474-2629

tors, which regulated the Ca^{2+} conductance.

Characterization of the Ca^{2+} current in granule cell from rat cerebellum Whole-cell recordings were obtained from neurons maintained for 2 to 14 d in culture. Because the Ca^{2+} current was too small in the granule cells, barium 20 mol · L^{-1} was usually used as the charge carrier in the experiment. All neurons exhibited high-voltage-activated (HVA) inward Ca^{2+} currents in response to content depolarizing pulses from − 80 mV to 0 mV after 2 DIC. The amplitude of the evoked Ca^{2+} current markedly increased with the time of culture; from 50 pA in maximal amplitude after 2 DIC could reach a maximal value of 300 − 350 pA after 10 − 15 DIC[7]. Our result was corresponding with the observation in the dissociated granule cells from rat cerebellum[8], and suggested that the density of Ca^{2+} channels increased with the age in culture. In addition, an age-dependent expression of HVA Ca^{2+} current during granule cell development had been investigated in cerebellar slices using whole-cell patch-clamp recordings from 7 − 24-d-old rats[9]. It demonstrated that the percentage of cell with a measurable HVA current and the size of HVA increased in parallel with granule cell maturation. At < 14 d, HVA current consisted of a fast- and slow-inactivating component, while at > 19 d only the slow-inactivating component remained.

Two distinct types of HVA Ca^{2+} channels, dihydropyridine (DHP)-sensitive and ω-conotoxine-sensitive channels, were identified by single channel recording in cell-attached patch and whole-cell recording in cerebellar granule cells of rat[10]. It was very interesting that the presence of each type of Ca^{2+} channel in such cells depended also on the time in culture[7,8]. The L-type Ca^{2+} channel, which was dihydropyridine agonist-sensitive, had a conductance of 18 pS, a half activation potential of > 10 mV and did not inactivate. This type of channel was the only type found during the first 4 d in culture and seemed to be the predominant Ca^{2+} channel types expressed in young granule cells. The N-type Ca^{2+} channel, which was dihydropyridine insensitive and ω-conotoxine-sensitive, had a conductance of 10 pS, a half activation potential < − 15 mV, and displayed a voltage-dependent inactivation. This second type of channel was found in cells more than 4 and 5 d in culture.

The relationship between synaptogenesis and expression of voltage-dependent current in cerebellar granule cells had been studied with whole-cell recording from cerebellar slices of 4 − 31-d-old rats[11]. Granule cells in the external granular layer, and nonconnected granule cells in the internal granular layer expressed outward current and inconstant, also small Ca^{2+} currents, but no fast Na^{+} currents. Most connected granule cell expressed Ca^{2+} and Na^{+} currents. These data indicated that the Ca^{2+} and Na^{+} channel development occurred after synapse formation, while outward K^{+} current began their development before. However, the data from single cell suggested that HVA Ca^{2+} channel not only changed their numbers, but also changed their gating and pharmacological properties with the development. The mechanism at the molecular level remained speculative, but the developmental changes of the HVA Ca^{2+} current must be related to the processes of granule cell maturation and excitability.

Activating of D_4 receptor inhibited an L-type Ca^{2+} current in cerebellar granule cell The dopamine receptors were now divided into two subfamilies, D_1-like receptor subtype and D_2-like receptor subtype. The D_2-like receptor subfamily includes the D_{2A}, D_{2B}, D_3, and D_4[12]. D_4 receptor was the most recent of dopamine receptor subtype identified. It might represent an important target for antipsychotics because their expression was enhanced in the schizophrenic brain[13]. But little was known in

cellular localization and multiple signaling system about the D_4 receptor, also no G protein coupling and no conductance changes had been reported to be associated with the activation of a constitutive D_4 receptor in any cerebral neuron. We used a combination of electrophysiology, pharmacology, and molecular biology approaches to investigate the role of a D_4 receptor in cultured granule cells from neonatal rat cerebellum[7].

Our result showed that dopamine 2 $\mu mol \cdot L^{-1}$ gave rise to an inhibition of Ca^{2+} current, an effect reversed upon washout. The current amplitude increased with the culture days, but evolution of the percentages of Ca^{2+} current inhibition and of cells responding to dopamine decreased with the time in culture. After application of nifedipine, dopamine had no apparent effect on the remaining dihydropyridine-resistant Ca^{2+} current. In contrast, after treatment with ω-conotoxin, the inhibition of residual current by dopamine was not significantly changed when compared with effect without treatment with ω-conotoxin. These results suggested that the L-type Ca^{2+} current was the only Ca^{2+} conductance to be controlled by dopamine in granule cell from young rat.

Dopamine receptor subtype was identified by molecular and pharmacological methods in our experiment. Expression of dopamine D_2, D_3, or D_4 receptors and β-actin mRNA at various stages of culture were quantified by competitive polymerase chain reaction (PCR). No signal corresponding to D_2 and D_3 receptor mRNA could be detected after 3, 7, or 14 d in culture, while PCR products corresponding to D_4 receptor mRNA appeared at all stages of the culture. In another way, the pharmacological profile of the dopamine response indicated that it was mediated by the D_4 receptor. The action of dopamine was mimicked by quinpirole, a D_2/D_3 and D_4 receptor agonist, but not by SKF38393, a D_1/D_5 receptor agonist. Application of the D_4-like receptor antagonist clozapine in the bath solution reduced the dopamine-evoked inhibition of Ca^{2+} current. The results together with the discovery of D_4 receptor mRNA strongly suggested the involvement of D_4 dopamine receptor subtype. Moreover, the inhibition of L-type Ca^{2+} current caused by dopamine was irreversible when the GTPγS was dialyzed via the patch pipette. If the cells were pre-incubated with PTX, even prolonged administration of dopamine had no effect on voltage-activated Ca^{2+} current. When cAMP was added to the pipette solution together with the phosphodiesterase inhibitor IBMX, the inhibition of dopamine was not significantly different from that recorded in the absence of cAMP and IBMX in the internal solution.

The D_2-like receptor was most likely the site of action for drugs used to treat schizophrenia. One of these drugs, clozapine, was distinct from other antipsychotics in that it did not produce the side effects of parkinsonism and tardive dyskinesias[14]. The good therapeutic index of clozapine might result from its partial D_4 selective[15]. Thus, it might be possible to find other antipsychotics free of extrapyramidal side effects from agents that selectively block D_4 receptors. To understand the D_4 receptor, it was necessary to find the function of D_4 receptor and D_4 receptor-mediated signaling events. Our study just demonstrated the presence of a functional dopamine D_4 receptor in cultured granule cells from neonatal cerebellum. It provided the first characterization of an electrophysiologic response mediated by this receptor subtype, and strongly supported a role for dopamine in cerebellar granule cell. In regard to the signal transduction pathways modulated by the D_4 receptor, some studies had been done primarily with a transfected Chinese hamster ovary cell line[16]. The experiment results indicated that D_4 receptor activation inhibited cAMP accumulation, potentiated the release of arachidonic acid in a dose-

ISSN 0253-9756 Acta Pharmacologica Sinica 中国药理学报 1999 Jan; 20 (1)
E-mail aps@server.shcnc.ac.cn Phn/Fax 86-21-6474-2629

dependent manner, and stimulated an amiloride-sensitive Na^+/H^+ exchanger. These studies revealed that D_4 receptors had the potential to activate multiple, *independent signaling event*. This multiple transduction pathway of D_4 receptor probably coupled to more than one type of G protein simile with D_2 receptor[17]. Thus, the reduction of Ca^{2+} current mediated by activating D_4 receptor of cerebellar granule cell may involve another signaling system with the exception of cAMP system.

It was also interesting what could be the role of the D_4 receptor in the cerebellum. Recently, using combined retrograde transport and tyrosine hydroxyl immunohistofluorescence, a dopamine pathway from ventral tegumental area to the cerebellar granule cell layer was identified[18]. Additionally, tyrosine hydroxylase immunoreactivity was detected in a small number of Purkinje cells[19]. These observations together with our study supported the existence of a dopaminergic system in the granule cell involving the D_4 receptor. Their excitability and transmitter synthesis might be regulated throughout this dopamine receptor subtype simile with that reported in the rat retina, in which dopamine inhibited melatonin synthesis in photoreceptor cells by activation of the D_4 receptor[20].

Activating pituitary adenylate cyclase activating polypeptide (PACAP) receptor increased Ca^{2+} currents in cerebellar granule cell PACAP was a member of the secretin/glucagon/VIP family of peptides and existed in two α-amidated forms, PACAP-27 and PACAP-38. They shared the same 27 amino-terminal amino acids and arised from a precursor peptide via post-transnational processing[21]. PACAP played an important physiologic role. At the pituitary level, PACAP stimulated adenylyl cyclase activity, and increased the release of several hormones such as growth hormone, ACTH, and prolactin[22]. PACAP-containing neurons and PACAP receptors were distributed in the adult rat brain, suggesting that PACAP did not solely act as a hypophysiotropic neurohormone but likely exerted *neurotransmitter activities*[23]. Our investigation would focus on the functions of PACAP receptors during development and relationship with Ca^{2+} channel in the cerebellum.

The ontogeny of PACAP binding sites in the rat cerebellum had been performed by quantitative autoradiography from birth to adulthood[24]. PACAP binding sites were present *in four layers*: the *internal granule cell* layer (IGL), external granule cell layer (EGL), the molecular layer, and the medulla. In the EGL and medulla, the concentration of PACAP binding sites was high at birth and regularly declined until the end of the third postnatal week. These transient occurrences of PACAP binding receptor in EGL and medulla suggested that PACAP may involve in the control of cell multiplication and differentiation. Concurrently, the presence of PACAP binding sites in mature granule cells of the IGL strongly suggested that PACAP act as a neurotransmitter in adult rat brain. The PACAP binding sites detected in the molecular layer between postnatal d 8 and d 25 were probably borne by the migrating immature granule cells that let the EGL to reach the IGL.

Based on the relative affinities for PACAP and VIP, PACAP binding sites had been divided into at least two types[25]. Type I PACAP receptors specifically binded to PACAP, whereas type II PACAP receptors binded with similar affinity to both PACAP and VIP. In the cerebellum, type I PACAP receptors were abundant[26]. The effects of activating type I PACAP receptor on second messenger systems had been studied in cultured granule cell from 8-d rat cerebellum. Both PACAP-27 and PACAP-38 induced a dose-dependent stimulation of cAMP production in immature granule cells[27]. PACAP also produced a rapid increase of IP_3 levels and a

concomitant decrease of PIP2 and PIP. Incubation of immature granule cells with pertussis toxin or the phospholipase C inhibitor U-73122 caused a reduction of the stimulatory effect of PACAP-38 on inositol phosphate formation. However, incubation of granule cells with forskolin, dbcAMP did not affect inositol phospholipid turnover. These data indicated that PACAP stimulated a phospholipase C through a pertussis toxin-sensitive G protein and independently through the adenylyl cyclase pathway.

The effects of PACAP on $[Ca^{2+}]_i$ in cultured granule cells had been directly investigated by microfluorimetry[28]. Both PACAP-38 and PACAP-27 caused a substantial increased in $[Ca^{2+}]_i$, while VIP had no effect on $[Ca^{2+}]_i$. Addition of egtazic acid or cadmium, or incubation of granule cells in Ca^{2+}-free medium decreased but did not abolish the stimulatory effect of PACAP on $[Ca^{2+}]_i$, suggesting PACAP induced mobilization of Ca^{2+} from intracellular stores. The $[Ca^{2+}]_i$ response to PACAP was not affected by forskolin or dbcAMP, indicating an involvement of cAMP-independent mechanism. However, the results on $[Ca^{2+}]_i$ could not exclude the effect of PACAP activating Ca^{2+} channel, just like reported by Chatterjee *et al*[29]. We thus investigated the action of PACAP on the Ca^{2+} channels currents in primary culture of cerebellar granule cell by using whole-cell recording[30]. The results showed that PACAP-38 and PACAP-27 reversibly increased HVA Ca^{2+} current, but had no effect on the current activation kinetics. In contrast, VIP at a same concentration could not evoke a response in the Ca^{2+} current. The increase of Ca^{2+} current caused by PACAP became irreversible with electrode containing $GTP_\gamma S$, while cell failed to induce any response to PACAP after addition of $GDP_\beta S$ to the intracellular solution or pre-incubated with PTX. In addition, the effect of PACAP on the Ca^{2+} channels was not modified when pipette contained cAMP and IBMX. These results indicated that in cultured granule cell from neonatal rat cerebellum, a pertussis toxin-sensitive G protein was implicated in the coupling PACAP receptor to activate Ca^{2+} channels, the G-protein-mediated signal transduction did not involve the adenylate cyclase system.

The mRNA expressions of type I PACAP receptor variants had been found in granule cells using the reverse transcription-polymerase chain reaction methodology[31]. The data suggested that PACAP-induced cAMP and inositol phosphate formation in cerebellar granule cells were mediated by two receptors, the PACAP-R and PACAP-R-hop variants, coupled to adenylate cyclase and phospholipase C, respectively. Our data indicated that the increase of $[Ca^{2+}]_i$ and Ca^{2+} current by PACAP in cerebellar granule cell were cAMP-independent, thus it was possible that PACAP increased intracellular Ca^{2+} content by activation of Ca^{2+} channel and mobilization of intracellular Ca^{2+} stores through the same PACAP-R-hop and phospholipase C-dependent transduction pathway.

Some studies had shown that PACAP was a potent regulator of cell proliferation, neurite outgrowth, and protein synthesis[32,33]. Recently, the relationship between PACAP receptor activation and apoptosis had been investigated in cultured cerebellar granule cells. The results demonstrated that PACAP could reduce apoptosis induced by serum deprivation and prevent apoptosis induced by low K^+ in cultured cerebellar cells[31]. To our knowledge, the extensive neuronal death occurred during the normal development of the nervous system. In the developing cerebellum, a loss of granule cells between postnatal d 5 and 9 was thought to regulate the granule cells to Purkinje cell stoichiometry[34]. Indeed, the number of granule cells in adult was directly proportional to

ISSN 0253-9756 Acta Pharmacologica Sinica 中国药理学报 1999 Jan; 20 (1)
E-mail aps@server.shcnc.ac.cn Phn/Fax 86-21-6474-2629

the number of Purkinje cells, indicating the existence of factors that regulated the survival of granule cells. PACAP receptor activation might represent one of the endogenous mechanisms that regulated survival of cerebellar granule cells. Activating HVA Ca^{2+} currents, however, might be an important and necessary role of PACAP as a neurotropic factor involved in the control of multiplication, differentiation, and migration of granule cells.

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小脑颗粒细胞的高电压激活钙电流及多巴胺 D_4 和垂体腺苷酸活化酶激活多肽受体对它的调节作用

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关键词 小脑; 多巴胺受体; PACAP 受体; 钙通道; 电生理学

摘要 小脑颗粒细胞是离体单细胞水平中枢神经元生物学研究的理想模型. 随着细胞发育, 其 HVA 钙电流的基因表达、门控性质和药理学特征发生明显变化, 提示钙电流涉及颗粒细胞的成熟和兴奋性的产生. 多巴胺通过激活膜上的 D_4 受体抑制 *L*-型钙电流, 这种抑制效应并不需要腺苷酸环化酶系统的参与. 功能性 D_4 受体的首次发现不仅有助于研究抗精神病药, 更揭示了多巴胺也参与小脑神经元之间的兴奋传递过程. PACAP 则通过激活其 I 受体增加钙内流和钙库的释放使胞浆内钙浓度提高, PACAP 的钙通道刺激效应可能需要 PLC 系统的介导, 并与颗粒细胞的成熟和成活有关.

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