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Molecular and Functional Diversity of Ion Channels and Receptors. Conference of New York Academy of Sciences, New York, May 14 – 17, 1998.

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The conference "Molecular and Functional Diversity of Ion Channels and Recep - tors" was held on May 14 to 17 at the New York University Medical Center.

The conference consisted of eight sessions (34 lectures) and two poster sessions, it was attended by ca. 300 participants.

PRESENTATIONS

Session One

The first session was devoted to glutamate receptors and chaired by **S. E. Heine-mann** (Salk Institute, San Diego, CA). **M. B. Kennedy** (Caltech, Pasadena, CA) spoke about signal transduction molecules of postsynaptic density (PSD) with a par - ticular emphasis on postsynaptic proteins. A total of seventeen different proteins have been isolated from PSD. One of the major proteins, p135 SynGAP, has been se - quenced; it is co-localized with *N*-methyl-D-aspartate (NMDA), but not γ-aminobuty-ric acid (GABA), receptors. CaM K II phosphorylates p135 SynGAP in the presence of Ca^{2+} and calmodulin. Postsynaptic fraction also contains phosphatase activity. Phosphatase I is highly concentrated: it is responsible for dephosphorylation.

O. P. Otterson (Institute for Basic Medical Sciences, Oslo, Norway) spoke about the arrangement of glutamate receptors in excitatory synapses. According to him, PSD is rich in (±)-2-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) and NMDA receptors. In cerebellum he finds no evidence for presynaptic NMDA recep - tors. Metabotropic receptors are not found in PSD. Delta $_2$ receptors are intermingled with AMPA receptors. Neurons are capable of targeting certain glutamate receptors to specific synapses.

S. Heinemann described kainate receptor-deficient mice. His group produced knock-out mice without the GluR 6 kainate receptor subunit. Kainate binding sites are

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absent in the CA3 region and the dentate nucleus of the hippocampus of "knock-out" mice. At the mossy fiber-CA3 synapse post-synaptic current is not detectable. The "knock-out" animals exhibit reduced locomotor activity and are resistant to kainate-induced seizures, but learn water maze tasks normally.

R. Nicoll (UCSF) discussed long term potentiation (LTP) and plasticity of excitatory synapses. During depolarization Na^+ and Ca^{2+} enter neurons through NMDA receptors. In synapses LTP redistributes synaptic strength. After LTP the synaptic failures are reduced. Inhibition of CaM K II blocks LTP. In the CA1 region MK 801 causes decay of synaptic responses.

H. Monyer (Max-Planck Institute, Heidelberg, Germany) discussed regulation of expression of AMPA and NMDA receptors in neurons. According to her, the GluR B subunit determines calcium permeability. GABAergic interneurons are involved in the synchronization of pyramidal cells. All interneurons have high levels of GluR D expression. NMDA receptor subunits NR_1, NR_{2B}, and NR_{2D} are expressed in the brain. The expression of the NR_{2A} subunit increases during development, and regulation of NR_{2A} expression facilitates cellular control during development.

M. Sheng (Mass. Gen. Hospital and Harvard Univ., Boston, MA) reviewed ion channel anchoring proteins and molecular organization of synapses. Among proteins that are known to anchor ion channels in the membrane, the best known are PSD 95, CRIPT, and PDZ. PSD 95 and CRIPT are associated with excitatory synapses. PSD 95 is also associated with microtubules. CRIPT is cysteine rich, interacts with PDZ1 and PDZ2, and is present in PSD. Many membrane and cytosolic proteins are known to bind to PDZs, including the NMDA R_2 subunit, Shaker K^+ channel, neurolgin, Ca^{2+} pump, APC, CRIPT, and others. Another protein, GIP, is present in PSD and is highly expressed in the early stages of development.

The session on Na^+ and Ca^{2+} channels was chaired by **T. Snutch** (Univ. of Brit. Columbia, Vancouver, Canada). He also lectured on molecular and functional diversity of Ca^{2+} channels. Many genes for Ca^{2+} channels have been identified: α_{1A} is the gene for P/Q type channels, its mutations are known to cause diseases such as familial migraine, episodic ataxia, and cerebral ataxia in humans, and "tottering" syndrome in mice. The phenotype for the α_{1B} gene is an N-type channel. A novel T-type channel is the phenotype for the α_{1G} gene. Genes for L-type channels are $\alpha_{1C, D, S}$. Mutation of the β_4 gene is responsible for "lethargic" mouse syndrome. Of particular interest to Snutch is the role of various gene fragments in the initiation of certain types of Ca^{2+} currents. His laboratory prepared many gene constructs that control the initiation of P- or Q-type currents.

A. C. Dolphin (Univ. College, London, UK) discussed the involvement of the N terminus of neuronal Ca^{2+} channels in G-protein modulation. Her group generated a series of α_{1B}/α_{1E} chimeric channels and studied the structural requirements of channels for G-protein modulation in rat brain. They concluded that the N terminals of α_{1B} and α_{1E} calcium channels subunits contain molecular determinants for G-protein inhibition.

E. Perez-Reyes (Loyola Univ. Chicago Med. School, Maywood, IL) lectured on the molecular characterization of T-type Ca^{2+} channels. T-type calcium channels inactivate more rapidly and at more negative potentials than L-type channels. They are resistant to rundown and insensitive to blockers of L-type channels. T-type channels are

formed by α_{1G} and α_{1H} genes. The α_{1G} gene is expressed primarily In the brain, and α_{1H} is found in the basal ganglia and striatum. The α_{1E} gene forms high-voltage, activated Ca^{2+} channels (HVA). The subunits of HVA do not appear to interact with the cloned T-type channels. T-type calcium channels control basal intracellular Ca^{2+} levels and appear to be coupled with K^+ channels. Abnormal T-type currents are found in epileptic brain, and antagonists of T-type current may be useful in the treatment of epilepsy.

R. W. Tsien (Stanford Univ., Stanford, CA) reviewed the functional role of diverse Ca^{2+} channels in synaptic transmission. His group is using antisense agents to calcium channel genes to block various calcium currents. α_{1E} Antisense blocks R-type, but not P/Q-type currents, while α_{1A} antisense blocks P/Q- and R-type currents. N-type and P/Q-type currents are important for synaptic transmission; they control Ca^{2+} entry presynaptically, thereby controlling transmitter release. P/Q-type currents appear to be more important than N-type currents at the human neuromuscular junction. L-type channels appear to play an important role in gene regulation and nuclear CREB phosphorylation in dendritic postsynaptic structures. Intracellular calcium signaling at the postsynaptic level involves translocation of calmodulin. L-type calcium channel antagonists (nifedipine and nimodipine) block this translocation and reduce the availability of calmodulin at the cell nucleus.

R. Llinas (New York University) was scheduled to speak about functions and oscillations mediated by specific Na^+ and Ca^{2+} channels in the central nervous system. He spoke instead primarily about T-type channels. According to him nerve cells have intrinsic oscillatory properties. The coherence of cellular electrical activity is controlled by ion channels. T-type calcium channels are critical for the coordination of oscillations of neuronal membranes and, therefore, for the normal neuronal function. The speed of oscillations is also controlled by K^+ channels. High frequency oscillations are produced by P/Q channels. The neuronal oscillations can be antagonized by Aga IVA, a known antagonist of P/Q channels.

The Keynote Lecture was delivered by **P. Goldman-Rakic** (Yale University, New Haven, CT). The title of her lecture was "From Channel Diversity to Higher Brain Function." She described her work with nonhuman primates involving single cell recordings in vivo from the neurons in prefrontal cortex. These neurons increase the firing rate in relation to the mnemonic trace of the preceding events (working memory); the integrity of these neurons appears to be essential for the memory tasks. The pyramidal neurons in the prefrontal area have dopaminergic, serotonergic, and GABAergic innervation and their excitability is modulated by dopamine, serotonin, and GABA. She examined the role of dopamine D_{1-5} and serotonin 5-HT_{2A} and 5-HT_3 receptors in the modulation of memory tasks using iontophoretically administered agonists and antagonists of these receptors. The density of D_1 receptors in the prefrontal cortex is high. The D_1 antagonist SCH 39166 enhanced firing of the neurons at low concentrations and inhibited it at higher concentrations. The D_2 antagonist raclopride had no effect on working memory neurons. Apical dendrites in raphe nucleus are rich in 5-HT_{2A} receptors. α-Methyl 5-HT enhanced firing of memory neurons, while the 5-HT_{2A} antagonist LU 53857 had an opposite effect. 5-HT_3 receptors are found in the interneurons, co-localized with calbindin receptors, but not with other 5-HT receptors. Dopamine modulates excitatory transmission primarily through D_1 receptors, and only

indirectly through D_2 receptors. Serotonin modulates excitatory transmission in pyramidal neurons; it inhibits transmission through 5-HT_{2A} receptors.

W. H. Catterall (Univ. of Washington, Seattle, WA) spoke about the interaction of presynaptic Ca^{2+} channels with SNARE proteins in neurotransmitter release. P/Q- and N-type calcium channels are located presynaptically, they control Ca^{2+} entry and, consequently, transmitter release. These channels bind to SNARE proteins in the cell membrane, including syntaxin, SNAP-25, and synaptotagmin. They bind to a synaptic protein interaction (synprint) site in the intracellular loop (between domains II and III) of the α_1 subunit of Ca^{2+} channels. The binding is Ca^{2+} dependent. The transmitter release is facilitated by interaction of SNARE proteins with presynaptic Ca^{2+} channels. This interaction brings synaptic vesicles closer to the Ca^{2+} channels and allows efficient transmitter release.

R. Reenan and his associates (Univ. of CT, Farmington) discussed RNA editing of the voltage-gated Na^+ channel in Drosophila. They identified four editing sites in the channels that are developmentally regulated and cloned a potential RNA editase, DRED.

Session Two

The next session was chaired by **B. Ganetzky** (Univ. of WI, Madison, WI). The first speaker was **M. Lazdunski** (CNRS, Valbonne, France). He spoke about the amiloride-sensitive super family of Na^+ channels and diseases associated with the mutations of these channels. The epithelial Na^+ channel is composed of α, β, and γ subunits. The α subunit alone can function as a channel. Mutations of β and γ subunits lead to Liddle syndrome. The acid-sensitive Na^+ channel ASIC is activated by H^+. ASIC is expressed in brain and dorsal root ganglion (DRG) cells; its homolog, DRASIC, is present only in DRGs. Both channels are likely to be involved in pain perception. Two other proteins, MDEG1 and MDEG2 modulate the functions of ASIC and DRASIC. Mutations of these proteins appear to be responsible for neuronal degeneration. The pH sensitivity of the mutant channels changes drastically with one amino acid replacement.

L. Salkoff (Washington Univ., St. Louis, MO) spoke about the impact of the *C. elegans* genome project on K^+ channel biology. The sequence of the *C. elegans* genome revealed a large number of K^+ channels in this organism. Eighty genes that encode K^+ channel subunits were identified. The channels were classified according to the number of membrane domains in three classes (2TM, 4TM, and 6TM channels), and each class was subdivided into families (6TM class has six families). These channels affect neuronal function and their diversity assures fine tuning of a single neuron function.

K. Wickman (Harvard Univ., Boston, MA) discussed the physiological role of GIRK potassium channels. G-protein-gated K^+ channels are formed by various combinations of four subunits: GIRK1, 2, 3, and 4. These channels appear to be involved in vagally mediated heart rate regulation. All four subunits are also expressed in brain. Wickman's group developed GIRK4 knock-out mice. The heart rate in these mice is

identical to that in control animals, but periodic irregularities of heart rate present in control animals are not observed in knock-outs.

B. Ganetzky discussed the EAG family of K^+ channels (Heag, Helk, and Herg). These are voltage-gated, outwardly rectifying K^+ selective channels. Mutation of the human gene for Herg is known to cause Long QT syndrome in humans, which can lead to ventricular fibrillation and sudden death. These channels are also expressed in brain and are likely to modulate neuronal excitability. They represent potential targets for neuroprotective drugs.

J. P. Adelman (Vollum Institute, Portland, OR) discussed structure and function of Ca^{2+} gating in small-conductance Ca^{2+} activated K^+ channels. These channels are apamin-sensitive and are present in various tissues, including brain. Two residues determine apamin sensitivity. The β subunit is likely to confer Ca^{2+} gating. Hippocampal SK channels exist in two probability modes (high and low). The SK1 channel in hippocampal neurons is not apamin sensitive. SK channels are highly expressed. It appears that calmodulin binds to SK channels. All cloned SK channels have the same sensitivity to Ca^{2+}.

B. Rudy (NYU) identified four mammalian genes ($Kv3_{1,2,3,4}$) that appear to be involved in the generation of the fast spiking properties and the regulation of synaptic transmission in the brain. These genes generate tetraethylammonium (TEA)-sensitive K^+ channels. $Kv3_2$ channels are found in dorsal thalamus and are thought to be involved in thalamo-cortical transmission.

O. Pongs (ZMNH, Hamburg, Germany) reviewed functional and molecular aspects of voltage-gated K^+ channel (Kv) β subunits. These subunits appear to increase Kv channel expression and to confer A-type behavior to non-inactivating Kv channels. Knock-out mice (without the Kvβ1.1 subunit) display reduced activity in hippocampal and striatal neurons and possibly altered cognition and motor control.

The session on nicotinic and serotonin receptors was chaired by **L. W. Role** (Columbia Univ. NYC). Her presentation was entitled "Heteromeric Complexes of α_5 and α_7 Subunits: Effect of Calcium and Potential Role in Nicotine-Induced Presynaptic Facilitation." Neuronal nicotinic receptors (nAchRs) have α- and β-type subunits that are encoded by multiple genes. There are at least seven α and three β subunits known. Receptors composed of different subunits are also pharmacologically different. Subunits $\alpha_{7,8,9}$ can function alone; other α subunits require β subunits to function. nAchRs differ in their calcium dependence. Nicotine enhances synaptic transmission at glutamatergic synapses in the central nervous system. At low concentrations (20 nM) nicotine acts presynaptically, while at high concentrations (20 μM) it also acts postsynaptically. Synaptic facilitation by nicotine decreases with repeated administration.

J. A. Dani (Baylor Coll. Mod., Houston, TX) spoke about nicotinic modulation of glutamate and GABA synaptic transmission in hippocampal neurons in slice and primary culture. He suggested that presynaptic nAChRs mediate Ca^{2+} influx, which enhances the release of glutamate and GABA. In primary hippocampal neurons in culture nicotine increases the release of glutamate and GABA. α-Bungarotoxin antagonizes the effects of nicotine on the transmitter release. Nicotine's effect appears to be mediated through the α_7 subunit of nAChRs.

C. Lena (Institut Pasteur, Paris, France) discussed the role of the β_2 subunit-containing nAChRs in the brain. The studies utilized knock-out mice lacking the β_2 subunit. Nicotine increases firing rate in dopamine neurons and increases brain dopamine levels in normal, but not knock-out mice. The reinforcing properties of nicotine appear to depend on the presence of the β_2 subunit in nAChRs.

R. Hen (Columbia Univ. NYC) discussed 5-HT knock-out mice as models of psychiatric disorders. Mice without functional 5-HT_{1A} receptor exhibit reduced exploratory behavior and fear adversive situations, but appear to be less vulnerable to despair in forced swim test. The author suggested that deficits of 5-HT_{1A} receptors may be responsible for some anxiety states.

P. J. Whiting (MSD, Harlow, U. K.) spoke about molecular and functional diversity of the $GABA_A$ receptor gene family. The receptor subtypes are assembled from at least seven different subunits; α, β, and γ subunits are present in most subtypes. The subunits confer distinct properties to the receptor subtypes. MSD group recently identified another member of the $GABA_A$ receptor gene family, the θ subunit, which contains 627 amino acids and is expressed in monkey brain. Its distribution correlates with that of tyrosine hydroxylase. θ-Containing receptors do not bind benzodiazepines with high affinity. The θ subunit alone does not function as a receptor, but $\alpha_1\beta_1\theta$ is a functional receptor.

J. M. Fritschy (Univ. of Zurich, Switzerland) reviewed differential regulation of $GABA_A$ receptor subtypes. α_1 and α_2 Subunits of $GABA_A$ receptors are found in different neurons. α_1 Subunits are found primarily in interneurons, β_2 subunits primarily in pyramidal cells. Brain-derived neurotrophic factor (BDNF) decreases cell surface immunoreactivity and the expression of $GABA_A$ receptor; it dephosphorylates β_2 and β_3 and γ_2 subunits. Phosphorylation appears to regulate cell surface expression of $GABA_A$ receptors. Expression of $GABA_A$ receptors is changed *in vivo* in epilepsy.

H. Betz (Max Planck Institute for Brain Research, Frankfurt, Germany) lectured on the structure and function of strychnine-sensitive glycine receptors (GlyR). Four genes encode different variants of the α subunit of GlyR. The receptor is located postsynaptically. Both α and β subunits are required for postsynaptic inhibition. The gating of GlyR is potentiated by Zn^{2+}. The anchoring protein gephyrin is required for the function of GlyR. Mutations of GlyR subunit genes can lead to motor neuron disorders in mice and humans (spasmodic mice and human hereditary startle disease).

J. L. Noebels (Baylor College of Medicine, Houston, TX) spoke about Ca^{2+} channel mutations and neurological diseases. A number of genetic diseases have now been associated with the mutations of subunits of voltage-dependent Ca^{2+} channels. Among them are familial hemiplegic migraine and episodic ataxia type 2. Both these diseases are consequences of mutation of the α_{1A} subunit. Autosomal dominant cellular ataxia (SCA6) is associated with polyglutamine expansion of the α_{1A} subunit. Tottering is also dependent on changes in the α_{1A} subunit. Abnormal β_4 subunit was associated with lethargic behavioral changes. Loss of functional β subunits leads to changes in P/Q type channel activity. Ca^{2+} channel mutants can alter gene expression and cause abnormal neuronal firing and hyperactivity.

R. Sprengel (Max Planck institute for Medical Research, Heidelberg, Germany) reported early onset of epilepsy in mice deficient in RNA editing of the AMPA receptor. Unlike the NMDA receptor, the AMPA receptor is usually poorly, or not at all

permeable to Ca^{2+}. Both NMDA and AMPA receptors are involved, however, in synaptic plasticity. The Heidelberg group generated three lines of mutant mice in which Ca^{2+} influx in pyramidal neurons was increased 2 to 9 times and mediated by AMPA receptors. These animals exhibit neurological dysfunction ranging from hyperactivity to lethargy. The severity of the dysfunction is correlated with the magnitude of Ca^{2+} influx. Animals with Na^+-impermeable, Ca^{2+}-permeable AMPA receptors develop epilepsy.

M. Sanguinetti (Univ. of Utah, Salt Lake City, Utah) discussed the functional consequences of mutations in delayed rectifier K^+ channels. Rectifier K^+ currents are major regulators of cardiac repolarization. Long QT syndrome (LQT) can be hereditary. Mutations of KVLQT1 or HERG genes that encode rectifier K^+ channels are the most common causes of LQT that can lead to increased risk of torsades de pointes and sudden death.

According to **N. Heitz** (Rockfeller Univ. NYC) neurodegeneration in lurcher mice results from a mutation in the $delta_2$ subunit of the glutamate receptor gene. During postnatal development of heterozygous lurcher mice, 90% of cerebellar Purkinje cells undergo apoptosis and die. Heitz and coworkers found that Purkinje cells in these animals display high membrane conductance, depolarized inward potential, and large inward current. The mutation in these animals involves a change of highly conserved alanine to a threonine in the transmembrane domain III of $delta_2$ subunit of glutamate receptor gene.

SELECTED POSTERS

At the two poster sessions 102 posters were presented. Most of them were devoted to molecular biology of ion channels, receptors, or their genes. The selection of posters for review here was based on the novelty of the material, the author's personal interests, and/or relevance of the subject to ion channel pharmacology.

S. Alagarsami et al. (Emory Univ., Atlanta, GA) findings suggest that NMDA reverses mGluR5 desensitization by activation of phosphatase, probably calcineurin. **A. Bullig et al.** (Univ. of Munich, Germany) identified a functional Na^+ channel of a neuroendocrine subtype in steroidogenic endocrine cells. According to **Y. Chen et al.** (NIH) the β_2 adrenergic receptor exerts local control of L-type calcium channels via a membrane-delimited pathway. **H. Dong et al.** (Johns Hopkins Univ., Baltimore, MD) demonstrated that glutamate receptor interacting protein (GRIP) is colocalized with AMPA receptors and GABAergic synapses and suggested that GRIP may be involved in the function of excitatory as well as inhibitory synapses. **L. K. Friedman and J. Veliskova** (Seton Hall Univ., Edison, NJ) reported that unilateral knockdown of the hippocampal $GluR_2$ subunit induces age-dependent seizures and reduces the survival of CA3 neurons in young rats. **B. E. Furman et al.** (Penn State Univ. Hershey, PA) found that by chronic intraperitoneal administration at 10 mg/kg nimodipine reduces tyrosine hydroxylase mRNA in the Purkinje cells of tottering mice. **S. Hering et al.** (Univ. of Innsbruck, Austria) reported that the sensitivity of Ca^{2+} channels for organic blockers is dependent on the intrinsic gating properties of the channel molecule. Mibefradil's action is less dependent on channel inactivation than the effects of

phenylalkylamines or benzothiazepines. According to **J. S. Kelly and H. Hecimovic** (Univ. of Edinburgh, Scotland) okadaic acid antagonizes the inhibitory action of internal GTR-γ-S on the Ca^{2+} current of dorsal raphe neurons but not that of 5-HT_{1A} receptor activation. **T. M. Lewis et al.** (Univ. College, London, UK) studied the structure-activity relationships of human glycine receptors and proposed that $M_1 - M_2$ and $M_2 - M_3$ loops form "hinges" that allow the allosteric signal transduction for gating of the pore-lining M_2 domain. **K. Kaupmann et al.** (Novartis, Basel, Switzerland) studied human $GABA_B$ R_1 receptors and demonstrated consistent functional coupling of $hGABA_BR_{1a\ and\ b}$ to GIRKs in mammalian cells. **M. Sassoe-Pognetto et al.** (Univ. of Turin, Italy) studied postsynaptic co-localization of gephyrin and $GABA_A$ receptors and concluded that gephyrin is likely to be involved in anchoring $GABA_A$ receptors in the postsynaptic membrane. **S. H. Schorge et al.** (Brown Univ., Providence, R. I.) demonstrated the interdependence of N and L Ca^{2+} channel signaling pathways in sympathetic neurons. Ca^{2+} entry via L channels stabilizes α_{1B} mRNA that encodes a component of N-channel protein providing a rapid mechanism for modulating N-type Ca^{2+} channel expression. **S. Srivastava et al.** (NYU) reported cloning and characterization of AMPA receptor interacting protein (ABP). It binds specifically to GluR2/3 and is 63 to 93% homologous to GRIP. ABP and GRIP represent a novel family of AMPA receptor anchoring proteins. **T. Varming and C. Mathieson** (NeuroSearch, Denmark) reported electrophysiological studies with a new selective AMPA receptor antagonist, SPD 502. SPD 502 was studied in mouse neurons cultured from neocortex. AMPA currents are inhibited by SPD 502 with an IC_{50} of 0.14 μM. *In vivo* SPD inhibited AMPA-induced single neuron spike activity with an ED_{50} of 12 μmol/kg by microiontophoretic administration. **K. A. Wafford** (MSD, Harlow, Essex, UK) mutated leucine to serine in the human $GABA_A$ β_2 subunit. This mutation resulted in a receptor that retains some spontaneous activity and is more sensitive to agonists. **J. Xia et al.** (Columbia Univ., NYC) studied molecular determinants of L-type calcium channel block by charged dihydropyridines (DHPs). They concluded that a charged headgroup restricts access of the attached DHP moiety to interaction residues and that interaction between the P-region glutamate residues and the charged headgroup contribute to the restricted access of the attached DHP moiety to key interaction residues. **L. Dwoskin et al.** (Coll. of Pharmacy, Univ. of KY, Lexington, KY) presented a novel class of subtype-selective nicotinic receptor antagonists that are expected to be valuable tools for probing the consequences of activating different subtypes of nicotinic receptors. **D. A. Gurley et al.** (Astra Arcus, Rochester, NY) compared the effects of the nicotine- and α_7-selective agonist AR-R 17779 on AChR α_7 expressed in *Xenopus* oocytes. AR-R 17779 is more potent and efficacious than nicotine in stimulating nAChR α_7 expressed in oocytes. It also lacks long-lasting inhibitory activity. **N. Meiri et al.** (NIH, Bethesda, MD) studied the effect of specific K^+ antisense knockdown on memory and LTP. They found that Shaker K^+ channel Kv1.1 is essential for hippocampal-dependent memory but not for LTP in rats, while Kv1.4, a presynaptic A-type voltage-dependent channel, is essential for LTP but not for memory. **R. B. Puchalsky et al.** (Monell Chemical Senses Center, Philadelphia, PA) cloned a novel ATP-regulated voltage-gated K^+ channel expressed in brain and taste buds of catfish. **V. E. S. Scott et al.** (Abbott Labs, Abbott Park, IL) described molecular and pharmacological properties of ATP-sensitive K^+ channels in bladder

smooth muscle. The channel activators elicit hyperpolarization responses in isolated bladder smooth muscle. Their order of potency is: P1075~BAY X 9228 > (–)cromakalim~ZD-6169-pinacidil > (+)cromakalim > diazoxide. **F. Sgard et al.** (Synthelabo, Rueil Malmaison, France) studied the expression of the nicotinic receptor subunit mRNA in dopaminergic neurons of rat brain. They found that $\alpha_{3,5,6}$ and β_4 subunits are selectively expressed in substantia nigra, while $\alpha_{2,3,5,6,7}$ and β_4 subunits are selectively expressed in the ventral tegmental area. **D. Wunderler et al.** (Merck Res. Labs. Rahway, NJ) reported that correolide, a triterpene from roots of Spachea correae, blocks K^+ channels (Kv1.3, 1.2, 1.2, 1.4, and 1.6) in human lymphocytes. It is more potent against Kv1.3 than other channels. It appears to block channels preferentially in open or inactivated states. **R. Zwart et al.** (Utrecht Univ., The Netherlands) found that physostigmine and atropine potentiate and inhibit $\alpha_4\beta_4$ nAChRs, respectively, by the same mechanism. **T. D. Jorgensen et al.** (NeuroSearch, Glostrup, Denmark) reported that a cloned human intermediate-conductance Ca^{2+}-activated K^+ channel is inhibited by clotrimazole or charybdotoxin and activated by 1-ethyl-2-benzimidazolinone (EBIO). They also developed a fluometric imaging-based high throughput assay for the characterization of novel pharmacological modulators of the h1K channel.