ION CHANNELS AND NUCLEAR PORE CHANNEL GATING

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Calcium, sodium, potassium, zinc, magnesium etc & all other ion channels carry vital biological functions with respective signaling playing great role in plasma, heart beats, dopamine & many other functions either directly by particle, ions or by their waves. There are three main types of ion channels, i.e., voltage-gated, extracellular ligand-gated, and intracellular ligand-gated along with two groups of miscellaneous ion channels. Ion channels facilitate passive movement of ions across biological membranes and are essential for life. Ion-channel engineering approaches help elucidate structure-function mechanisms of proteins. Engineered ion channels are important tools for probing and manipulating cell biology. Voltage-gated channels respond to perturbations in cell membrane potential, and are highly selective for a specific ion, i.e., Na+, K+, Ca2+, and Cl-, Others are Ligand-Gated Ion Channels (LGIC),'Cys-Loop" LGIC, Ionotropic Glutamate Receptors., P2X Receptors. .Mechano-Sensitive Ion Channels. Their ions &ion channels enable the flow of electrical signals through the body.

Nuclear envelope (NE) cisternal Ca2+ and cytosolic ATP are required for nuclear-pore-complex-(NPC-) mediated transport of DNAs, RNAs, transcription factors and other large molecules. Isolated cardiomyocyte nuclei, capable of macromolecular transport (MMT), have intrinsic NPC ion channel behavior.Ca2+ and IP3 waves may convert the NE into an effective Ca2+ barrier and, consequently, affect the regulation of gene activity and expression through their feedback on MMT and NPCC gating. Thus, [Ca2+] NE regulation by intracellular messengers is an effective mechanism for synchronizing gene activity and expression to the cellular rhythm. We found that calcium ion channels & some other ion channels play great roles in all biological activities & require great investigations in field of nuclear medicines as most of diseases are caused by abnormal functions of ions & ion-channels in lives. Behind biology is physics or nuclear physics & all require simultaneous quite clear definitions in this respect.

Charged particle therapy is a rapidly developing way for tumor treatment. During irradiation, the primary beam interacts with tissues nuclei results in the production of radioactive isotopes and secondary particles emission, e.g. electrons, gammas and neutrons. Estimation of the treatment effect of secondary radiation using only Monte Carlo is not precise and, depends on the type of radiation, the direct measurement of it is difficult. During presentation the experimental results of induced radioactivity will be discussed. Such experiments have been done at the Institute of Nuclear Physics PAS. Moreover method of neutron energy spectrum measurement will be presented. Measured spectra and geometry of experimental set-ups allow appraising the cross-

section of reactions that occurs in the target and then calculate the dose that is deposited in human tissues as a result of therapy aside from the primary beam.

1-Calcium, sodium, potassium, zinc, magnesium etc & all other ion channels carry vital biological functions with respective signaling plays great role in plasma, heart beats, dopamine & many other functions either directly by particle, ions or by their waves. There are three **main** types of **ion channels**, i.e., voltage-gated, extracellular ligand-gated, and intracellular ligand-gated along with two groups of miscellaneous **ion channels**.

Ion channels facilitate passive movement of **ions** across biological membranes and **are** essential for life. **Ion**-**channel** engineering approaches help elucidate structure-function mechanisms of these proteins. Engineered **ion channels are** important tools for probing and manipulating cell biology.

2-Types of Ion Channels in the Body-

Voltage-Gated **Ion Channels**. Voltage-gated **channels** respond to perturbations in cell membrane potential, and are highly selective for a specific **ion**, i.e., Na+, K+, Ca2+, and Cl-. ...

Ligand-Gated **Ion Channels** (LGIC) ,“Cys-Loop” LGIC. ,Ionotropic Glutamate Receptors,P2X Receptors. ,Mechano-Sensitive **Ion Channels**. etc

These **ions** enable the flow of electrical signals through the **body**. Electrolytes play an **important role in the body**; they regulate the osmotic pressure in cells and help maintain the function of muscle and nerve cells.

Examples of **ionic** compounds in **everyday life** include table salt, baking soda, lye, Epsom salt, and bleach. There are many **examples** of **ionic** compounds in **everyday life**. **Ionic** compounds consist of atoms joined together by **ionic** bonds. Many **ionic** compounds are binary compounds formed by a metal and a nonmetal.

3-**Nuclear envelope (NE) cisternal Ca2+ and cytosolic ATP** are required for nuclear-pore-complex-(NPC-) mediated transport of DNAs, RNAs, transcription factors and other large molecules. Isolated cardiomyocyte nuclei, capable of macromolecular transport (MMT), have intrinsic NPC ion channel behavior. The large ion conductance (gamma) activity of the NPC channel (NPCC) is blocked by the NPC monoclonal antibody mAb414, known to block MMT, and is also silenced during periods of MMT. In cardiomyocytes, neither cytosolic Ca2+ nor ATP alone directly affects NPCC gating. To test the role of Ca2+ and ATP in NPCC activity, we carried out the present patch-clamp study with the pipette attached to the outer NE membrane of nuclei isolated from cultured Dunning G prostate cancer cells. Our investigations demonstrate that in these isolated nuclei neither cytosolic Ca2+ nor ATP alone directly affects NPCC gating. However, when simultaneously applied to the bath and pipette, they transiently silence NPCC activity through stimulation of MMT by raising the Ca2+ concentration in the NE cisterna ([Ca2+]NE). Our fluorescence microscopy observations with nuclear-targeted macromolecular fluorochromes (B-phycoerythrin and plasmid for the enhanced green fluorescence protein EGFP, pEGFP-C1) and with FITC-labeled RNA support the view that channel silence accompanies MMT. Repeated Ca2+ loading of the NE with Ca2+ and ATP, after unloading with 1-5 microM inositol 1,4,5-trisphosphate (IP3), thapsigargin (TSG) or 5 mM BAPTA or EGTA, failed to affect channel gating. This result indicates that other factors are involved in this phenomenon and that they are exhausted during the first cycle of NE Ca2+ loading/unloading--in agreement with current theories of NPC-mediated MMT. The results explain how Ca2+ and

IP3 waves may convert the NE into an effective Ca2+ barrier and, consequently, affect the regulation of gene activity and expression through their feedback on MMT and NPCC gating. Thus, [Ca2+]NE regulation by intracellular messengers is an effective mechanism for synchronizing gene activity and expression to the cellular rhythm.

Role of the nuclear envelope in calcium signaling-

The endoplasmic reticulum (ER) is the major Ca(2+) store inside the cell. Its organisation in specialised subdomains allows the local delivery of Ca(2+) to specific cell areas on stimulation. The nuclear envelope (NE), which is continuous with the ER, has a double role: it insulates the nucleoplasm from the cytoplasm and it stores Ca(2+) around the nucleus. Furthermore, all the constituents of the signalling cascade leading to Ca(2+) mobilisation are found in the NE; this allows the nuclear Ca(2+) to be regulated autonomously. On the other hand, cytosolic Ca(2+) transients can propagate within the nucleus via the nuclear pore complex. The variations in nuclear Ca(2+) concentration are important for controlling gene transcription and progression in the cell cycle. Recent data suggest that invaginations of the NE modify the morphology of the nucleus and may affect Ca(2+) dynamics in the nucleus and regulate transcriptional activity.

4-**Regulation of calcium signals in the nucleus by a nucleoplasmic reticulum-**

Calcium is a second messenger in virtually all cells and tissues. Calcium signals in the nucleus have effects on gene transcription and cell growth that are distinct from those of cytosolic calcium signals; however, it is unknown how nuclear calcium signals are regulated. Here we identify a reticular network of nuclear calcium stores that is continuous with the endoplasmic reticulum and the nuclear envelope. This network expresses inositol 1,4,5-trisphosphate (InsP3) receptors, and the nuclear component of InsP3-mediated calcium signals begins in its locality. Stimulation of these receptors with a little InsP3 results in small calcium signals that are initiated in this region of the nucleus. Localized release of calcium in the nucleus causes nuclear protein kinase C (PKC) to translocate to the region of the nuclear envelope, whereas release of calcium in the cytosol induces translocation of cytosolic PKC to the plasma membrane. Our findings show that the nucleus contains a nucleoplasmic reticulum with the capacity to regulate calcium signals in localized subnuclear regions. The presence of such machinery provides a potential mechanism by which calcium can simultaneously regulate many independent processes in the nucleus.

5-Sodium-calcium exchanger complexed with GM1 ganglioside in nuclear membrane transfers calcium from nucleoplasm to endoplasmic reticulum

The inner membrane of the nuclear envelope (NE) was previously shown to contain a Na/Ca exchanger (NCX) tightly linked to GM1 ganglioside that mediates transfer of nucleoplasmic Ca(2+) to the NE lumen and constitutes a cytoprotective mechanism. This transfer was initially observed with isolated nuclei and is now demonstrated in living cells in relation to subcellular Ca(2+) dynamics. Four cell lines with varying expression of NCX and GM1 in the NE were transfected with cameleon-fluorescent Ca(2+) indicators genetically targeted to NE/endoplasmic reticulum (ER) and nucleoplasm to monitor [Ca(2+)](ne/er) and [Ca(2+)](n) respectively. Cytosolic Ca(2+) ([Ca(2+)](cyt)) was indicated with fura-2. Thapsigargin caused progressive loss of [Ca(2+)](ne/er), which was rapidly replaced on addition of extrinsic Ca(2+) to those cells

containing fully functional NCX/GM1: differentiated NG108-15 and C6 cells. Reduced elevation of [Ca(2+)](ne/er) following thapsigargin depletion occurred in cells containing little or no GM1 in the NE: undifferentiated NG108-15 and NG-CR72 cells. No change in [Ca(2+)](ne/er) due to applied Ca(2+) was seen in Jurkat cells, which entirely lack NCX. Ca(2+) entry to NE/ER was also blocked by KB-R7943, inhibitor of NCX. [Ca(2+)](n) and [Ca(2+)](cyt) were elevated independent of [Ca(2+)](ne/er) and remained in approximate equilibrium with each other. Ca(2+) rise in the ER originated in the NE region and extended to the entire ER network. These results indicate the nuclear NCX/GM1 complex acts to gate Ca(2+) transfer from cytosol to ER, an alternate route to the sarcoplasmic/endoplasmic reticulum calcium ATPase pump. They also suggest a possible contributory mechanism for independent regulation of nuclear Ca(2+).

6-The role of nuclear Ca2+ in maintaining neuronal homeostasis and brain health-

Nuclear Ca2+ has emerged as one of the most potent mediators of the dialogue between neuronal synapses and the nucleus that regulates heterochromatin states, transcription factor activity, nuclear morphology and neuronal gene expression induced by synaptic activity. Recent studies underline the importance of nuclear Ca2+ signaling in long-lasting, activity-induced adaptation and maintenance of proper brain function. Diverse forms of neuroadaptation require transient nuclear Ca2+ signaling and cyclic AMP-responsive element-binding protein (CREB1, referred to here as CREB) as its prime target, which works as a tunable switch to drive and modulate specific gene expression profiles associated with memory, pain, addiction and neuroprotection. Furthermore, a reduction of nuclear Ca2+ levels has been shown to be neurotoxic and a causal factor driving the progression of neurodegenerative disorders, as well as affecting neuronal autophagy. Because of its central role in the brain, deficits in nuclear Ca2+ signaling may underlie a continuous loss of neuroprotection in the aging brain, contributing to the pathophysiology of Alzheimer's disease. In this Review, we discuss the principles of the 'nuclear calcium hypothesis' in the context of human brain function and its role in controlling diverse forms of neuroadaptation and neuroprotection. Furthermore, we present the most relevant and promising perspectives for future studies.

7-Carbon ion radiotherapy-

Carbon ion therapy (CIRT) uses particles more massive than protons or neutrons. Carbon ion radiotherapy has increasingly garnered scientific attention as technological delivery options have improved and clinical studies have demonstrated its treatment advantages for many cancers such as prostate, head and neck, lung, and liver cancers, bone and soft tissue sarcomas, locally recurrent rectal cancer, and pancreatic cancer, including locally advanced disease. It also has clear advantages to treat otherwise intractable hypoxic and radio-resistant cancers while opening the door for substantially hypo-fractionated treatment of normal and radio-sensitive disease.

8-**Synthetic brain cells that store 'memories' are possible, new model reveals**

Created a computer model of artificial neurons that could produce the same sort of electrical signals neurons use to transfer information in the brain; by sending ions through thin channels of water to mimic real ion channels, the researchers could produce these electrical spikes.
To generate an action potential, a neuron starts to let in more positive ions, which are attracted to the negative ions inside of the cell. The electrical potential, or voltage across the cell membrane, causes doorways on the cell called voltage-gated ion channels to open, raising the charge even more before the cell reaches a peak and returns to normal a few milliseconds later.

The signal is then transmitted to other cells, enabling information to travel in the brain. To mimic voltage-gated ion channels a modeled a thin layer of water between sheets of graphene, which are extremely thin sheets of carbon. The water layers in the simulations were one, two, or three molecules in depth, which was characterized as a quasi-two-dimension slit. Wanted to use this two-dimensional environment because particles tend to react much more strongly in two dimensions than in three, and they exhibit different properties in two dimensions. On applying an electric field to the channel, the ions in the water formed worm-like structures. As the team applied a greater electric field in the simulation, these structures would break up slowly enough to leave behind a "memory," or a hint of the elongated configuration. When the researchers ran a simulation linking two channels and other components to mimic the behavior of a neuron, they found the model could generate spikes in electrical activity like action potentials, and that it "remembered" consistent properties in two different states — one where ions conducted more electricity and one where they conducted less. In this simulation, the "memory" of the previous state of the ions lasted a few milliseconds, around the same time as it takes real neurons to produce an action potential and return to a resting state. This is quite a long time for ions, which usually operate on timescales of nanoseconds or less. In a real neuron, an action potential equates to a cellular memory in the neuron; our brains use the opening and closing of ion channels to create this kind of memory.

9-Study finds unleashing Treg cells may lead to treatments for multiple sclerosis

A certain protein prevented regulatory T cells (Tregs) from effectively doing their job in controlling the damaging effects of inflammation in a model of multiple sclerosis (MS), a devastating autoimmune disease of the nervous system. A new study illuminates the important role of Piezo1, a specialized protein called an ion channel, in immunity and T cell function related to autoimmune neuroinflammatory disorders. We found that Piezo1 selectively restrains Treg cells, limiting their potential to mitigate autoimmune neuroinflammation, Genetically deleting Piezo1 in transgenic mice resulted in an expanded pool of Treg cells, which were more capable of effectively reducing neuroinflammation and with it the severity of the disease.

T cells rely on specialized proteins, like Piezo1, to detect and respond to various diseases and conditions including bacterial infections, wound healing, and even cancer. Uncontrolled T cell activity, however, can give rise to autoimmune disorders in which the immune system attacks normal cells in the body. Tregs constantly curate immune responses and play a critical role in preventing autoimmunity. Given the demonstrated ability of Piezo1 to restrain Treg cells, we believe that inhibiting Piezo1 could lead to new treatments for neuroinflammatory disorders, like MS. Piezo1 conducts ions when cells are subjected to mechanical forces. Research over the last decade has shed light on the role of Piezo1 in regulating vital physiological functions including red blood cell (RBC) volume, blood pressure, vascular development, bone formation, and differentiation of neural stem cells. However, its role in modulating immune response has not been appreciated before. And, while it was known that calcium conducting ion channels, like Piezo1, direct various aspects of T cell function, researchers were surprised to find that Piezo1 was not essential for a whole host of T cell functions that rely on calcium, such as lymph node homing, interstitial motility, activation, proliferation, or differentiation into effector T cells. The role of Piezo1 appears to be quite specific to Tregs. Therefore, targeting Piezo1 might be a new and ideal strategy to cure MS while preserving the immune system's ability to fight new infections. Further investigation of the function of Piezo1 is needed to understand therapeutic potential, and to more fully understand the processes through which cells sense and respond to mechanical stimuli during immune responses.

10-Aussie scientists see life-saving potential in spider venom-

A group of Australia-based scientists are looking to venom from a deadly native spider to actually save lives, by halting the harmful effects of heart attacks. Researchers used venom from a type of funnel-web spider—among the world's deadliest species—in a drug they hope can soon be taken to human trials. So far the experimental medicine has only been lab-tested.

The venom helped stop the body sending a "death signal" after a heart attack, which causes cells to die. After a heart attack, blood flow to the heart is reduced, resulting in a lack of oxygen to heart muscle. The lack of oxygen causes the cell environment to become acidic, which combine to send a message for heart cells to die. Despite decades of research, no one has been able to develop a drug that stops this death signal in heart cells, which is one of the reasons why heart disease continues to be the leading cause of death in the world. The team has successfully used a protein from spider venom on beating human heart cells that were exposed to heart-attack stresses. The Hi1a protein from spider venom blocks acid-sensing ion channels in the heart, so the death message is blocked, cell death is reduced, and we see improved heart cell survival. It is hoped the drug could help not only prevent heart damage and save lives, but improve the quality of donated hearts during transplants. Previous research has indicated funnel-web spider venom may also be useful in curbing damage from strokes.

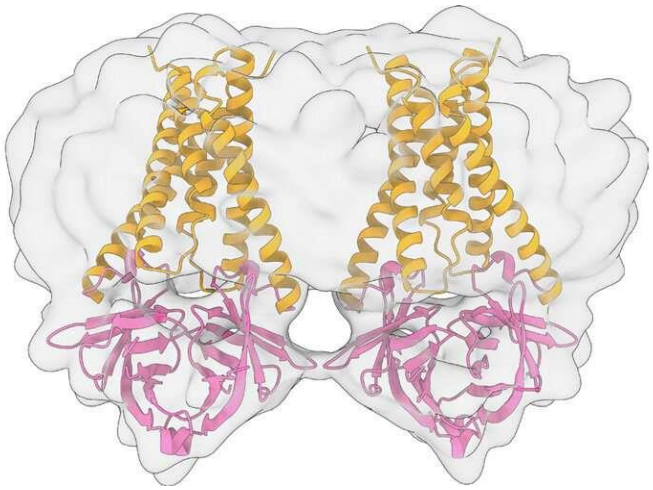
11-New insight into photosynthesis could help grow more resilient plants-

Plants store energy in the thylakoid membrane, a key structure to photosynthesis in plant leaves. Plants convert sunlight into usable energy through photosynthesis, but constantly adjust where and how they store the self-made energy based on light level, temperature, moisture and other factors. Figuring out how plants make these adjustments could improve our understanding of how they perform in the field and help develop new plants that can withstand rising temperatures from climate change. Energy conversion from sunlight and energy storage happens in specialized thylakoid membranes in chloroplasts in leaves. In leaves, plants pump protons from one side of the thylakoid membrane to the other generating a gradient of positive and negative charges. To regulate this energy storage, ion channels control the fluctuation in amount of energy available. Understanding this complex process could be the key to feeding people around the world on a warming planet. Photosynthesis is very powerful. If it's not controlled, it can produce too much energy, which creates dangerous molecules that can kill a plant. Engineering plants with better photosynthetic control would mean those plants could survive in sunnier, warmer conditions. The scientists shined a variety of lights on leaves and measured the changes in absorption and fluorescence. We illuminate leaves with different light intensities to create excited states in pigments, The leaf then changes its absorption and fluorescence properties that we measure; telling us what is going on in the leaf.

12-Unusual coronavirus protein is potential drug target to fight COVID-19-

The SARS-CoV-2 virus contains a gene that codes for a strange protein that could be a good target for drugs to fight COVID-19 and possibly other coronavirus infections. When the virus injects its genome into a cell, the so-called ORF3a gene is expressed to make a protein that moves to the surface of the cell and looks like an ion channel—a passage all cells have for ions like calcium to move in and out as they communicate with other cells. The protein is nothing like other ion channels known to science. For one thing, it's half a channel—it only pierces the cell membrane halfway. It also has an unusual fold not seen in other ion channels. While no one

knows why the virus carries a gene to make an ion channel—and a strange one, at that—By knocking out the ORF3a gene in SARS-CoV-2 and a related ORF3a gene in the original SARS virus, SARS-CoV-1, the severity of the disease is reduced, at least in animal models.



The 3a protein of the SARS-CoV-2 virus doubles up as a dimer when it is embedded in a cell membrane, serving as a channel for calcium ions. A drug that blocks the ion channel—though it also blocks other ion channels—and have identified mutations in the ORF3a gene that alter channel function. The 3a protein is the smallest membrane protein channel that has been imaged by cryoEM, which has rapidly become the best way to determine the 3D structure of molecules, down to the level of individual atoms and the water molecules that surround them. Brohawn continues to research the 3a protein and two other potential ion channels—called E and 8a —in the SARS-CoV-2 genome, both to understand how they work and to find potential drugs to inactivate them. The virus uses these ion channels to take over human and animal epithelial cells and neurons. Many viruses interfere with calcium signaling in cells, which may help them take over the cells' molecular machinery and force them to make millions of copies of the virus instead of daily cellular housekeeping.

13-Researchers have finally seen how some of them bind to odor molecules—yielding new insights into one of the most mysterious and versatile senses-

SMELL, RATHER THAN sight, reigns as the supreme sense for most animals. It allows them to find food, avoid danger, and attract mates; it dominates their perceptions and guides their behavior; it dictates how they interpret and respond to the deluge of sensory information all around them. Yet olfaction might also be the least well understood of our senses, in part because of the complexity of the inputs it must reckon with. What we might label as a single odor—the smell of coffee in the morning, of wet grass after a summer storm, of shampoo or perfume—is often a mixture of hundreds of types of chemicals. For an animal to detect and discriminate between the many scents that are key to its survival, the limited repertoire of receptors on its olfactory sensory neurons must somehow recognize a vast number of compounds. So an individual receptor has to be able to respond to many diverse, seemingly

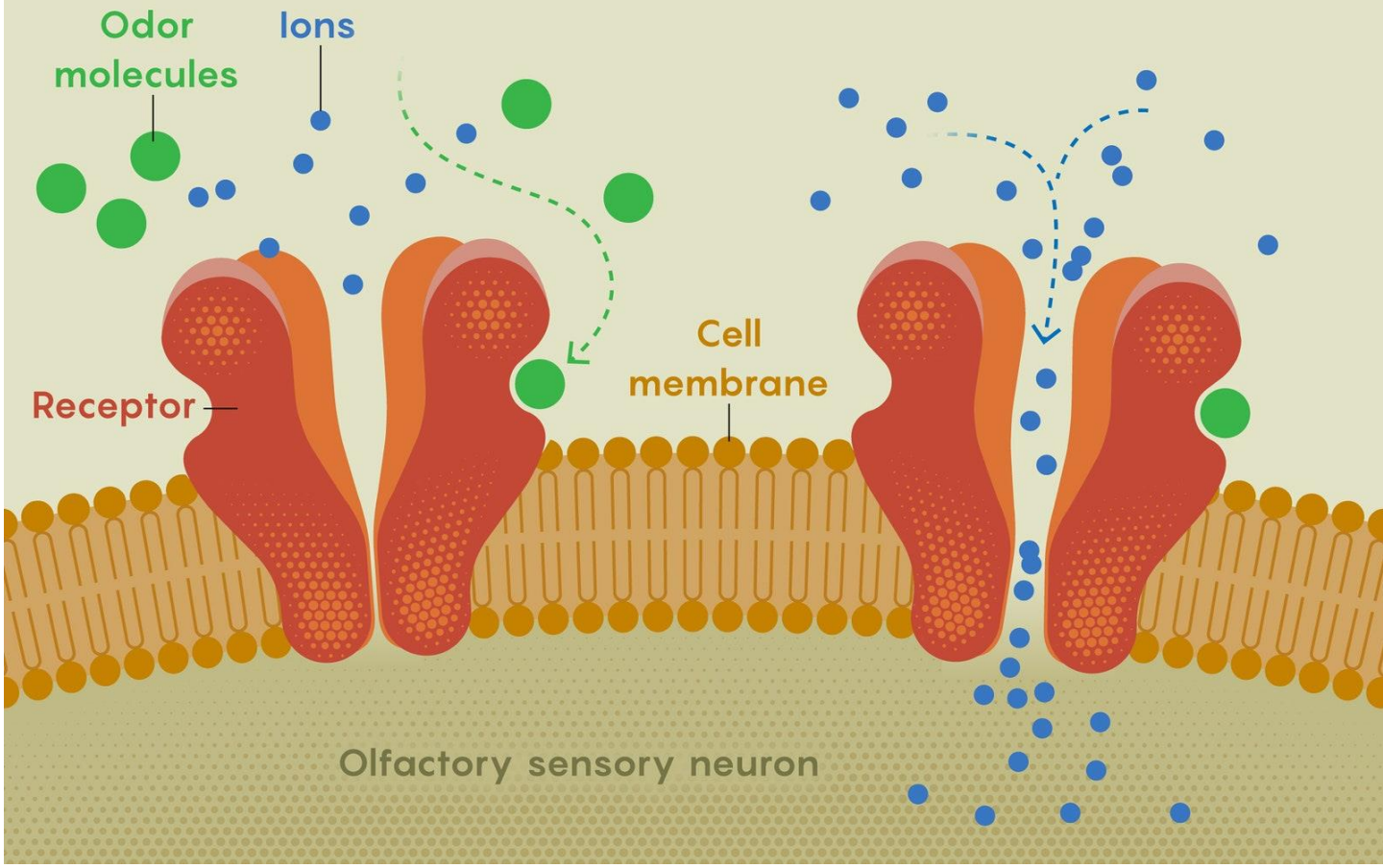
unrelated odor molecules. That versatility is at odds with the traditional lock-and-key model governing how selective chemical interactions tend to work. Something has to fit precisely in a site, and then it changes the [protein's atomic arrangement], and then it works. No one's ever actually seen with their eyes what it looks like when an odor binds to a receptor. Animals identify and discriminate among astronomical numbers of smells. It also sheds light on key principles of receptor activity that might have far-reaching implications—for the evolution of chemical perception, for our understanding of how other neurological systems and processes work, and for practical applications like the development of targeted drugs and insect repellents. In insects, olfactory receptors are ion channels that activate when an odor molecule binds to them. They may be the largest and most divergent family of ion channels in nature, with millions of variants across the world's insect species. So they must carefully balance generality against specificity, staying flexible enough to detect an enormous number of potential odors while being selective enough to reliably recognize the important ones, which could differ considerably from one species or environment to another.

Signaling a Scent

The complex process of olfaction begins when the chemicals that constitute an odor interact with receptors on the surface of olfactory sensory neurons. In insects, those receptors are ion channels.

1. An odor molecule binds to a receptor on a sensory neuron.

2. The central pore in the receptor opens, and ions flow into the neuron, activating it.



They looked at the structure of a jumping bristletail olfactory receptor in three different configurations: by itself, and bound to either a common odor molecule called eugenol (which smells like clove to humans) or the insect repellant DEET. They then compared those structures, down to their individual atoms, to understand how odor binding opened the ion channel, and how a single receptor could detect chemicals of very different shapes and sizes.

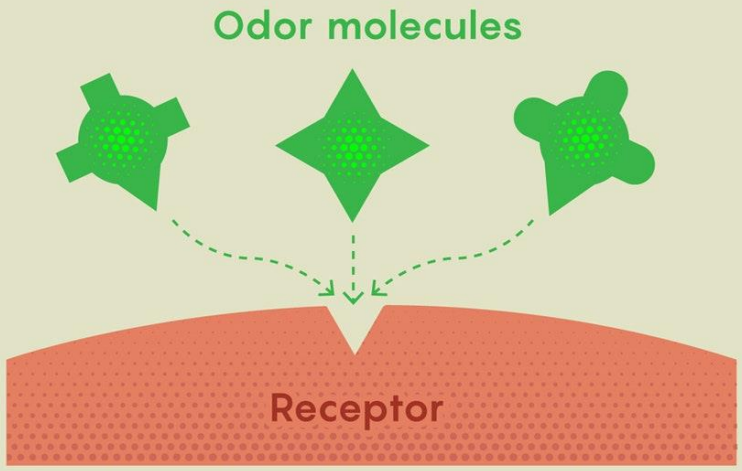
The researchers found that although DEET and eugenol don't have much in common as molecules, they both docked at the same site within the receptor. That turned out to be a deep, geometrically simple pocket, lined with many amino acids that facilitate loose, weak interactions; eugenol and DEET took advantage of different interactions to lodge within it. Further computational modeling showed that each molecule was able to bind in many different orientations—and that many other kinds of odor compounds, though not all, could bind to the receptor in a similar way. This was no lock-and-key mechanism, but a one-size-fits-many approach.

One Lock With Many Keys

Animals have a finite repertoire of olfactory receptors but must recognize an astronomical number of scents. Several theorized mechanisms could explain how the receptors achieve that flexibility.

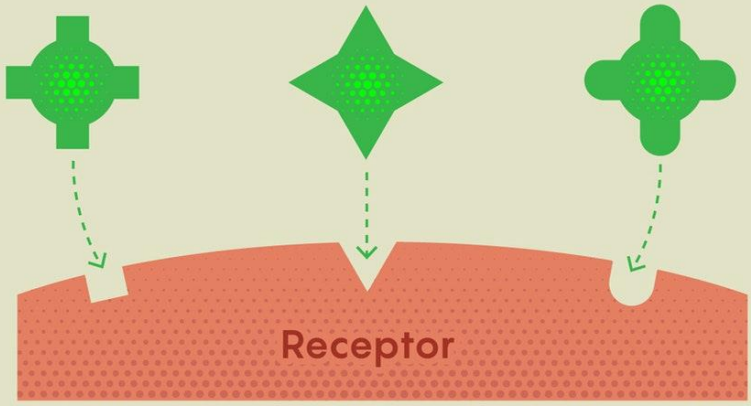
HYPOTHESIS 1

The receptor responds to any molecule that has a specific chemical feature.



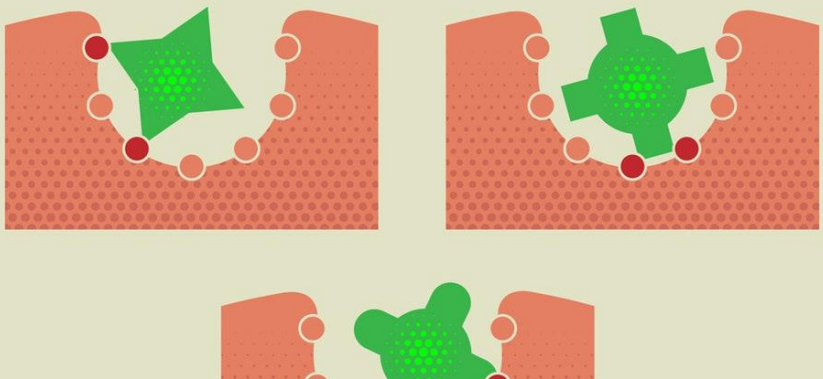
HYPOTHESIS 2

A receptor may have multiple binding sites for different chemical features on different odor molecules.



HYPOTHESIS 3

New work in insects shows that a receptor can respond to an odor molecule as a whole. Molecules can connect



The receptor is doing a more holistic recognition of the molecule, as opposed to just detecting any specific structural feature. On introducing changes to the receptor's pocket, they found that mutations of even a single amino acid were enough to alter its binding properties. And that, in turn, was enough to affect the receptor's interactions with many compounds, entirely reconfiguring what the receptor responded to. Widening the pocket, for instance, increased its affinity for DEET, a larger molecule, while decreasing its affinity for eugenol, which may not have been able to fit as snugly due to its smaller size. Such changes would have many downstream effects on the receptor's broader odor-detecting palette, too, which the researchers were not set up to identify. Insect olfactory receptors can generally evolve so rapidly and diverge so much among species. Every insect species may have evolved "its unique repertoire of receptors that are really well suited to its particular chemical niche. It tells us that more is going on than just the idea that receptors loosely interact with a bunch of ligands. A receptor built around a single binding pocket, with a response profile that can be retuned by the smallest of tweaks, could speed up evolution by freeing it to explore a broad spectrum of chemical repertoires. The architecture of the receptor also supported this view. It consisted of four protein subunits loosely bound at the channel's central pore, like the petals of a flower. Only the central region needed to be conserved as the receptor diversified and evolved; the genetic sequences governing the rest of the receptor units were less constrained. This structural organization meant the receptor could accommodate a wide degree of diversification. Such light evolutionary constraints at the receptor level probably impose substantial selective pressure downstream on the neural circuits for olfaction: Nervous systems need good mechanisms for decoding the messy patterns of receptor activity. Insects use many other classes of ion channel olfactory receptors, including ones that are much more complex and much more specific than those of the jumping bristletail. In mammals, the olfactory receptor is not even an ion channel; it belongs to an entirely different family of proteins. Neuromodulators like dopamine to those that are affected by various kinds of anesthetic. If many different kinds of proteins bind to receptors through flexible, weak interactions within some type of pocket, that principle could guide rational drug design for various diseases, particularly neurological conditions. The mosquito is still the deadliest animal on Earth" because of the diseases it carries..

14-Brainless Embryos Suggest Bioelectricity Guides Growth-

It's not just the brain that uses bioelectric signaling — the whole body does. All cell membranes have embedded ion channels, protein pores that act as pathways for charged molecules, or ions. Differences between the number of ions inside and outside a cell result in an electric gradient — the cell's resting potential. Vary this potential by opening or blocking the ion

channels, and you change the signals transmitted to, from and among the cells all around. Neurons do this as well, but even faster: To communicate among themselves, they use molecules called neurotransmitters that are released at synapses in response to voltage spikes, and they send ultra-rapid electrical pulses over long distances along their axons, encoding information in the pulses' pattern, to control muscle activity. They decided to express a specific ion channel called HCN2, which acts differently in various cells but is sensitive to their resting potential. Levin likens the ion channel's effect to a sharpening filter in photo-editing software, in that "it can strengthen voltage differences between adjacent tissues that help you maintain correct boundaries. It really strengthens the abilities of the embryos to set up the correct boundaries for where tissues are supposed to go.To make embryos express it, the researchers injected messenger RNA for HCN2 into some frog egg cells just a couple of hours after they were fertilized. A day later they removed the embryos' brains, and over the next few days, the cells of the embryo acquired novel electrical activity from the HCN2 in their membranes. Experiments on tadpoles reveal the influence of the immature brain on other developing tissues, which appears to be electrical, according to Levin and his colleagues. Photo A shows the appearance of normal muscle in young tadpoles. In tadpoles that lack brains, the muscles fail to develop the correct form (B). But if the cells of brainless tadpoles are made to express ion channels that can restore the right voltage to the cells, the muscles develop more normally (C).

15-Development of the world's first digital model of a cancer cell

Lung tumor example-

Pathological changes in cell membrane voltage, particularly during the cell cycle, are fundamental to cancer development and progression. Ion channels connect the outside to the inside of a cell. They enable the exchange of ions such as **potassium, calcium or sodium** and thereby regulate the membrane potential. Changes in the composition of ion channels, as well as altered functional behaviour of the same, can result in disruptions in cell division, possibly even affecting cell differentiation and thus transforming a healthy cell into a diseased (carcinogenic) cell. For digital cancer cell model, the example of the human lung adenocarcinoma cell line A549. The computer model simulates the rhythmic oscillation of the membrane potential during the transition between cell cycle phases and enables prediction of the changes in membrane potential that are caused by drug-induced switching on and off of selected ion channels. So we get information about the effects of targeted interventions on the cancer cell.

16-Freezing cancer cells during growth or inducing them to commit suicide-

The activity of certain ion channels can also drive the division of diseased cells and thus accelerate tumor growth. If ion channels are now manipulated in a targeted manner, as is the case with new, promising agents and drugs, the cell membrane voltage and thus the entire electrophysiological system can be thrown off track, so to speak. This could be used to arrest cancer cells at a certain phase in the cell cycle, but also to induce premature cell death

(apoptosis). One could "freeze" cancer cells while they are growing or induce them to commit suicide.

17-In plant cells, a conserved mechanism for perceiving mechanical force resides in unexpected location-

Minuscule tunnels through the cell membrane help cells to perceive and respond to mechanical forces, such as pressure or touch. A new study in the journal *Science* is among the first to directly investigate what one type of these mechanosensitive ion channels is doing in the tip-growing cells in moss and pollen tubes of flowering plants. Mechanosensitive ion channels are paths, or tunnels, through cell membranes that respond to mechanical forces. Under certain forces a channel opens, allowing the flow of ions across the membrane.

18-The structural basis of odorant recognition in insect olfactory receptors-

Olfactory systems must detect and discriminate amongst an enormous variety of odorants1. To contend with this challenge, diverse species have converged on a common strategy in which odorant identity is encoded through the combinatorial activation of large families of olfactory receptors, thus allowing a finite number of receptors to detect a vast chemical world. Here we offer structural and mechanistic insight into how an individual olfactory receptor can flexibly recognize diverse odorants. We show that the olfactory receptor *Mh*OR5 from the jumping bristletail4 *Machilis hrabei* assembles as a homotetrameric odorant-gated ion channel with broad chemical tuning. Using cryo-electron microscopy, we elucidated the structure of *Mh*OR5 in multiple gating states, alone and in complex with two of its agonists—the odorant eugenol and the insect repellent DEET. Both ligands are recognized through distributed hydrophobic interactions within the same geometrically simple binding pocket located in the transmembrane region of each subunit, suggesting a structural logic for the promiscuous chemical sensitivity of this receptor. Mutation of individual residues lining the binding pocket predictably altered the sensitivity of *Mh*OR5 to eugenol and DEET and broadly reconfigured the receptor's tuning. Together, our data support a model in which diverse odorants share the same structural determinants for binding, shedding light on the molecular recognition mechanisms that ultimately endow the olfactory system with its immense discriminatory capacity.

The olfactory system faces a unique challenge amongst sensory modalities owing to the inordinate complexity of the chemical world. Whereas light waves vary continuously in amplitude and frequency, odorants differ discretely along an enormous number of dimensions in their molecular structure and physicochemical properties. Consequently, just three photoreceptors are sufficient to sense the entire spectrum of visible light, but large repertoires of olfactory receptors appear to be necessary to detect and discriminate amongst the diversity of chemicals in the environment. In mammals, odour detection is mediated by G-protein-coupled receptors that signal through canonical second-messenger cascades. By contrast, insects detect volatile chemicals using a unique class of odorant-gated ion channels consisting of two subunits: a conserved co-receptor (Orco) subunit and a highly divergent odorant receptor (OR) subunit that contains the odorant-binding site and confers chemical sensitivity to the heteromeric complex. Although mammals and insects rely on distinct molecular mechanisms for odour detection, they share a common neural logic for olfactory perception based on the combinatorial activation of distinct ensembles of olfactory receptors and associated sensory neurons. Central to this sensory coding strategy is that most individual ORs detect a variety of structurally and chemically diverse odorants. However, in the absence of a structural model, how such flexible chemical recognition is achieved has remained unknown. Whether the broad chemical tuning of

ORs reflects the presence of multiple odorant-binding sites that differ in their chemical specificity or a single promiscuous binding pocket is not known. Furthermore, which structural or chemical features of odorants are recognized by a receptor remains unclear. In this study, we leveraged the evolutionary diversification of insect ORs to elucidate the structures of a homomeric receptor from a basal insect species bound to different ligands. A single receptor can detect a wide array of odorants through a single promiscuous binding site that recognizes the overall physicochemical properties of each odorant rather than being tuned to any of their specific structural or molecular features, suggesting a structural basis for flexible chemical recognition. Olfactory receptor tuning thus depends on the stereochemistry of its ligands25,26, but does not adhere to the classic lock-and-key mechanism that governs many receptor–ligand interactions. Odour discrimination is thus transformed from a biochemical problem at the receptor level to a neural coding problem within the brain. The evolution of the insect olfactory system demonstrate that *Mh*ORs can function as homomeric odorant-gated channels, supporting the proposal that they lie at the ancestral origin of the insect olfactory receptor family, which expanded massively across insect lineages to emerge as possibly the largest and most divergent class of ion channels in nature.

19-In female sheep, the drug—also known as sildenafil—was able to suppress an arrythmia called Torsades de Pointes within 90 seconds by reducing the frequency of irregular heart rhythms caused by abnormal handling of calcium. The drug could treat other arrythmias as well. Although calcium is a key driver of the heart's pumping action, its overload can be a root cause of arrythmias. Viagra was able to suppress the mechanism in the cell which causes calcium overload. When a small amount calcium enters a myocyte, it triggers the Sarcoplasmic Reticulum (SR)—a calcium store—to release a larger quantity of calcium. When there is heart disease, the SR can become overloaded with calcium which in turn makes the heart beat at the wrong time- when it is supposed to be resting between beats. The mechanism is part of an enzyme pathway inside the cell involving PDE5 and activating a protein called protein kinase G which impacts on the arteries in the penis allowing blood to pump into it. A similar mechanism exists around the muscle cells of the heart but has never been studied until now. This study suggests that the enzyme PDE5, which is suppressed by Viagra, may also play a key role in causing abnormal heart rhythms that arise from an overload of calcium in sheep heart cells. This could be important because the electrical behavior in these cells is similar to that of human heart cells. PDE5 inhibition suppresses ventricular arrhythmias by reducing SR Ca^{2+} content.

20-Conclusion-We see in all biological functions ion channels are involved. Nuclear medicines have great prospects in this regard.