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Texto 1:

Optogenetics: From Light-Sensitive Algae to the Control of Brain Activity

The human brain is an extraordinarily complex biological system, composed of billions of neurons that communicate through electrical and chemical signals. These cells form highly interconnected networks responsible for essential functions such as memory, emotions, movement, learning, and behavior. Understanding how specific groups of neurons contribute to these functions has been one of the greatest challenges in neuroscience.

For many years, researchers relied on methods that allowed them to record brain activity or stimulate relatively large populations of neurons. Although these approaches provided valuable information, they presented an important limitation: observing that a particular group of neurons becomes active during a behavior does not necessarily demonstrate that those neurons are responsible for producing that behavior. In other words, establishing a correlation between neuronal activity and a physiological response is not the same as demonstrating a causal relationship.

A major advance in overcoming this limitation came from the development of optogenetics, a technique that combines genetic engineering and light-based stimulation to control the activity of selected cells. The discoveries that made this approach possible were recognized with the 2026 Nobel Prize in Physiology or Medicine, awarded jointly to Karl Deisseroth, Peter Hegemann, and Georg Nagel.

The development of optogenetics began with investigations into how microorganisms respond to light. Peter Hegemann studied the behavior of the unicellular green alga *Chlamydomonas reinhardtii*, which can detect light and adjust its movement in response to environmental illumination. Together with Georg Nagel and other collaborators, he investigated light-sensitive proteins present in these organisms. Their research led to the characterization of channelrhodopsins, a family of membrane proteins that function as light-gated ion channels.

One particularly important protein, channelrhodopsin-2 (ChR2), responds to blue light. When exposed to an appropriate wavelength, the protein changes its conformation and opens a channel across the cell membrane. Positively charged ions can then enter the cell, modifying its electrical properties. In neurons, this process can produce membrane depolarization and trigger action potentials. Thus, light can be converted into an electrical signal through a specific membrane protein.

The importance of this discovery extended far beyond the study of algae. Karl Deisseroth and his collaborators recognized that light-sensitive proteins could be introduced into mammalian neurons through genetic techniques. Once these cells expressed channelrhodopsin, they became responsive to light. By directing blue light toward the modified neurons, researchers could rapidly control their electrical activity. This represented a fundamental innovation because it allowed the manipulation of specific neuronal populations rather than the nonspecific stimulation of large groups of cells.

The combination of genetic targeting and optical stimulation provided an unprecedented level of experimental precision. Genetic techniques determine which cells express the light-sensitive protein, while optical stimulation determines when these cells are activated. Other light-sensitive proteins, including inhibitory opsins, have also been developed or adapted, allowing researchers not only to activate neurons but also to reduce or suppress their activity.

This ability to manipulate neural circuits has transformed neuroscience. Instead of simply observing which brain regions are active during a particular behavior, researchers can selectively activate or inhibit specific neuronal populations and investigate the consequences. For example, they can examine whether activating a particular circuit produces a behavioral response or whether inhibiting it prevents that response. Such experiments provide stronger evidence about the functional roles of individual neural pathways.

Optogenetics has been applied to the investigation of memory, motivation, emotions, sleep, and motor control. It has also become an important tool for studying neurological

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and psychiatric disorders, including Parkinson's disease, epilepsy, and depression. Furthermore, its applications are not limited to the brain, since light-controlled approaches can also be used to investigate cellular and physiological processes in other tissues.

Despite its considerable potential, optogenetics presents technical challenges. Researchers must introduce the appropriate genetic material into the desired cells and deliver light to the target tissue with sufficient precision. In addition, the expression of foreign proteins and the delivery of light must be carefully controlled to avoid unwanted biological effects. Although the technique is primarily used as a research tool, experimental clinical applications are being investigated, including approaches to restore visual function in individuals with certain retinal diseases.

The history of optogenetics illustrates how basic research can lead to unexpected technological advances. Studies initially focused on understanding how a microscopic organism responds to light eventually provided scientists with a powerful method to investigate the complex communication networks of the mammalian brain. By transforming light into a tool for controlling cellular activity, the work of Hegemann, Nagel, and Deisseroth opened new possibilities for understanding biological mechanisms and developing future therapeutic strategies.

1). De acordo com o texto, qual foi a principal contribuição da optogenética para a investigação científica do sistema nervoso?

A) Permitir a identificação de todas as conexões anatômicas entre os neurônios sem a necessidade de procedimentos experimentais.
B) Substituir completamente os métodos eletrofisiológicos tradicionais por técnicas exclusivamente genéticas.
C) Permitir a manipulação seletiva da atividade de populações neuronais, possibilitando investigar relações causais entre a atividade de circuitos e determinados comportamentos.
D) Demonstrar que todos os comportamentos humanos são controlados por grupos específicos de neurônios que respondem à luz.
E) Permitir o registro simultâneo de todos os sinais elétricos produzidos pelo cérebro em condições fisiológicas.

2). A descoberta da channelrhodopsin em algas representa um exemplo de como a pesquisa básica pode contribuir para avanços em outras áreas da ciência. Qual alternativa melhor explica essa relação?
A) A proteína foi inicialmente descoberta em neurônios de mamíferos e posteriormente identificada em algas como uma forma de confirmar sua função.
B) A investigação de um mecanismo de resposta à luz em organismos unicelulares possibilitou o desenvolvimento de uma ferramenta para controlar a atividade elétrica de células nervosas.
C) A pesquisa demonstrou que as algas e os neurônios apresentam exatamente os mesmos mecanismos de comunicação celular.
D) A descoberta permitiu substituir a engenharia genética por mecanismos naturais de absorção de luz presentes em todos os tecidos animais.
E) O estudo das algas demonstrou que a atividade neuronal depende exclusivamente da disponibilidade de luz no ambiente.

3). Um pesquisador observa que determinado grupo de neurônios apresenta aumento de atividade durante um comportamento alimentar. Entretanto, ele deseja demonstrar se esses neurônios realmente participam da produção desse comportamento. Considerando as informações do texto, qual abordagem experimental seria mais apropriada?
A) Medir novamente a atividade desses neurônios durante o comportamento, aumentando o número de animais analisados.
B) Comparar a atividade desses neurônios em animais submetidos a diferentes condições nutricionais, sem interferir diretamente em sua atividade.
C) Introduzir uma proteína sensível à luz nesses neurônios e avaliar se sua ativação ou inibição modifica o comportamento alimentar.
D) Identificar a quantidade de neurotransmissores presentes no tecido cerebral, sem avaliar a atividade neuronal.
E) Determinar a localização anatômica dos neurônios e assumir que sua atividade está diretamente relacionada ao comportamento observado.

4). O texto menciona que, além das proteínas capazes de ativar neurônios, existem opsinas que podem reduzir ou suprimir sua atividade. Qual é a principal consequência científica dessa possibilidade?

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A) Permite investigar apenas os mecanismos responsáveis pela inibição neuronal, excluindo o estudo da atividade excitatória.
B) Demonstra que todas as proteínas sensíveis à luz possuem exatamente o mesmo mecanismo de ação.
C) Permite comparar experimentalmente as consequências da ativação e da inibição de circuitos neuronais, ampliando a investigação de suas funções.
D) Torna desnecessária a introdução de material genético nas células, pois todas as células nervosas respondem naturalmente à luz.
E) Impede a investigação de relações causais, pois a inibição neuronal não produz alterações comportamentais mensuráveis.

5). Considerando o potencial terapêutico da optogenética e as limitações mencionadas no texto, qual alternativa apresenta a interpretação mais adequada sobre suas aplicações clínicas?
A) Como a técnica permite controlar neurônios com luz, sua utilização clínica já pode substituir os tratamentos farmacológicos convencionais para doenças neurológicas.
B) A necessidade de introduzir material genético nas células demonstra que a técnica não apresenta potencial para aplicações terapêuticas.
C) As dificuldades de direcionamento genético e de entrega de luz indicam que a técnica ainda exige aprimoramentos, embora seus princípios já ofereçam possibilidades para o desenvolvimento de novas estratégias terapêuticas.
D) A utilização clínica da optogenética depende exclusivamente do desenvolvimento de fontes de luz mais intensas, independentemente de questões relacionadas à expressão proteica.
E) O fato de a técnica ser utilizada principalmente em pesquisas demonstra que seus resultados não podem contribuir para a compreensão de doenças humanas.

Texto 2:
Induced Pluripotent Stem Cells: Reprogramming Cell Identity and Opening New Possibilities in Biomedical Research

For many years, scientists believed that the identity of a mature cell was relatively stable. A skin cell, for example, performs functions very different from those of a neuron or a cardiac muscle cell. Although almost all cells in the human body contain essentially the same DNA, they express different sets of genes, which determine their structure and function. This specialization is known as cellular differentiation. However, an important question remained: could a mature cell be reprogrammed to return to a less specialized state?
A major breakthrough came in 2006, when Japanese researcher Shinya Yamanaka and his colleagues demonstrated that mouse somatic cells could be reprogrammed into a pluripotent state by introducing a small group of transcription factors. In 2007, the approach was successfully applied to human cells. These reprogrammed cells became known as induced pluripotent stem cells, or iPSCs. The discovery changed the understanding of cellular identity and created new possibilities for studying human biology and developing therapeutic strategies.
The original reprogramming method involved four transcription factors: Oct4, Sox2, Klf4, and c-Myc. These factors are commonly referred to as the Yamanaka factors. They regulate gene expression and help establish the molecular program characteristic of pluripotent cells. By introducing them into differentiated cells, researchers can activate genes associated with pluripotency and suppress parts of the gene-expression program responsible for the original cell identity. As a result, some cells gradually acquire properties similar to those of embryonic stem cells.
Pluripotency is the ability of a cell to differentiate into almost any cell type of the adult body, including neurons, cardiomyocytes, hepatocytes, and pancreatic cells. However, pluripotent cells are not equivalent to totipotent cells, which can generate all embryonic and extraembryonic tissues required for the development of a complete organism. This distinction is important because iPSCs have broad developmental potential, but they do not normally possess the full developmental capacity of a fertilized egg.
Cellular reprogramming is not simply a process of changing the shape or function of a cell. It involves extensive modifications in gene regulation and epigenetic organization. Epigenetic mechanisms, including DNA methylation and histone modifications, influence which genes are accessible and active without changing the underlying DNA sequence. During reprogramming, many of these epigenetic marks must be remodeled so that the cell can establish a new transcriptional identity. This process is complex and may be incomplete in some cells.

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One important advantage of iPSC technology is that pluripotent cells can be generated from adult tissues, such as skin fibroblasts or blood cells. Consequently, researchers can obtain cells from individuals with specific genetic diseases and reprogram them into iPSCs. These cells can then be directed to differentiate into cell types affected by the disease. For example, iPSCs obtained from a patient with a neurological disorder may be differentiated into neurons, allowing scientists to investigate cellular abnormalities that are difficult to study directly in the living human brain. This approach is particularly valuable for disease modeling. Researchers can compare cells derived from healthy individuals with those obtained from patients carrying disease-associated mutations. By analyzing differences in cell morphology, gene expression, metabolism, and cellular function, scientists can investigate the mechanisms underlying disease development. In some cases, gene-editing technologies such as CRISPR-Cas9 can be used to correct a specific mutation in patient-derived iPSCs. Comparing corrected and uncorrected cells provides an opportunity to investigate whether the genetic alteration is responsible for a particular cellular phenotype.

Another important application is drug discovery and toxicity testing. iPSC-derived cells can be used to evaluate the effects of candidate compounds on human cellular models. For instance, cardiomyocytes generated from iPSCs may help identify compounds that interfere with cardiac electrical activity or damage cardiac cells. Similarly, hepatocyte-like cells can be used to investigate potential liver toxicity. These approaches may provide information that is not always obtained from animal models or conventional cell lines. Nevertheless, iPSC-derived cells do not necessarily reproduce all the characteristics of fully mature cells in the human body.

In addition to producing individual cell types, researchers can use iPSCs to generate three-dimensional structures known as organoids. Organoids are self-organizing cellular systems that reproduce some structural and functional characteristics of specific organs. Brain, intestinal, liver, and cardiac organoid models have been developed to investigate aspects of human development and disease. Although these structures do not reproduce the complete complexity of real organs, they provide experimental systems in which cellular interactions and biological processes can be studied in greater detail.

Despite their potential, iPSC technology has important limitations. Reprogramming is generally inefficient, meaning that only a fraction of the starting cells may successfully acquire pluripotency. In addition, different iPSC lines can show considerable variability in their ability to differentiate into specific cell types. Some cells may retain epigenetic features of their original tissue, a phenomenon known as epigenetic memory. This residual memory may influence their behavior and differentiation potential.

Safety is another major concern, particularly when iPSCs are considered for clinical applications. Genetic abnormalities can arise during reprogramming or prolonged cell culture. Furthermore, undifferentiated pluripotent cells may form tumors if transplanted into patients. Therefore, therapeutic applications require careful evaluation of genomic stability, differentiation efficiency, cell purity, and the absence of potentially harmful undifferentiated cells. Standardized production methods and rigorous quality-control procedures are essential before these cells can be widely used in medicine.

An additional consideration is the possibility of immune rejection. Because iPSCs can be generated from a patient's own cells, they may offer an advantage for autologous transplantation. However, using patient-derived cells does not guarantee that the resulting differentiated cells will be completely free from immune recognition. Alternatively, banks of iPSC lines from selected donors may provide cells compatible with a larger number of patients, although immune compatibility remains an important issue.

Overall, induced pluripotent stem cells represent a powerful tool for biomedical research. They have changed how scientists investigate human development, model diseases, and evaluate potential treatments. Although important technical and safety challenges remain, improvements in reprogramming methods, genome editing, cell differentiation, and quality control are expanding the possibilities of this technology. The central contribution of iPSCs is not simply the production of new cells, but the ability to connect an individual's genetic background with experimental models of human biology and disease.

6). Um pesquisador obtém fibroblastos da pele de um paciente com uma doença neurológica genética, reprograma essas células em iPSCs e, posteriormente, induz sua diferenciação em neurônios. Qual é a principal vantagem científica dessa estratégia experimental?

A) Permitir a reprodução de todo o sistema nervoso humano em uma placa de cultura.

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B) Garantir que os neurônios reproduzam todas as manifestações clínicas da doença.
C) Possibilitar a investigação de fenótipos celulares associados à doença em um modelo celular humano que apresenta o contexto genético do paciente.
D) Eliminar a necessidade de células-controle, uma vez que células derivadas do paciente são suficientes para estabelecer causalidade.
E) Garantir que todos os neurônios diferenciados sejam geneticamente idênticos aos neurônios de indivíduos saudáveis.

7). O texto explica que a tecnologia CRISPR-Cas9 pode ser utilizada para corrigir uma mutação em iPSCs derivadas de pacientes. Por que a comparação entre células corrigidas e não corrigidas é particularmente útil?
A) Porque a correção necessariamente aumenta a taxa de proliferação de todas as iPSCs.
B) Porque permite aos pesquisadores determinar se a alteração genética contribui para o fenótipo celular observado, mantendo sob controle grande parte do contexto genético do paciente.
C) Porque as células corrigidas não precisam mais passar por diferenciação no tipo celular afetado pela doença.
D) Porque demonstra que todas as doenças genéticas são causadas por uma única mutação.
E) Porque a tecnologia CRISPR-Cas9 elimina completamente a possibilidade de alterações genéticas durante o cultivo celular.

8). De acordo com o texto, por que células derivadas de iPSCs podem ser úteis na descoberta de fármacos e na avaliação de toxicidade?
A) Porque substituem completamente os modelos animais e os ensaios clínicos na avaliação de novos medicamentos.
B) Porque reproduzem todas as características fisiológicas de órgãos humanos maduros em qualquer condição experimental.
C) Porque fornecem modelos celulares humanos que podem ser utilizados para investigar os efeitos de compostos candidatos, incluindo sua potencial toxicidade em tecidos específicos.
D) Porque garantem que compostos considerados seguros em testes in vitro também serão seguros em pacientes.
E) Porque impedem a ocorrência de efeitos adversos dos medicamentos por meio da correção de variações genéticas nas células testadas.

9). O texto identifica a memória epigenética residual como uma das limitações da tecnologia de iPSCs. Qual é a interpretação mais adequada desse fenômeno?
A) As células reprogramadas podem conservar algumas características epigenéticas do tecido de origem, o que potencialmente influencia sua capacidade de diferenciação.
B) As células reprogramadas sempre preservam integralmente a sequência de DNA do tecido original, incluindo todas as mutações, sem qualquer possibilidade de modificação.
C) A memória epigenética significa que as iPSCs são incapazes de expressar genes associados à pluripotência.
D) Refere-se à perda permanente de todas as informações epigenéticas durante a reprogramação celular.
E) Demonstra que a identidade celular é determinada exclusivamente pela sequência de DNA, e não pela regulação da expressão gênica.

10). Com base nos parágrafos finais, qual conclusão representa melhor o estágio atual da tecnologia de iPSCs?
A) As iPSCs já constituem um tratamento universalmente estabelecido para doenças genéticas e degenerativas.
B) A principal limitação das iPSCs é a incapacidade de gerar células diferenciadas a partir de tecidos adultos.
C) O uso de iPSCs derivadas do próprio paciente elimina todos os riscos associados ao transplante e à rejeição imunológica.
D) A tecnologia apresenta valor limitado para a pesquisa biomédica, pois as células derivadas de iPSCs não conseguem reproduzir nenhum fenótipo associado a doenças.
E) As iPSCs oferecem oportunidades importantes para a pesquisa biomédica e para futuras terapias, mas sua aplicação clínica exige avanços em segurança, reprodutibilidade, diferenciação celular e controle de qualidade.