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REVIEWS

From 'molecules of life' to new therapeutic approaches, an evolution marked by the advent of artificial intelligence: the cases of chronic pain and neuropathic disorders

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The large families of the molecules of life are at the origin of the discovery of new compounds with which to treat disease. The arrival of artificial intelligence (AI) has considerably modified the search for innovative bioactive drugs and their therapeutic applications. Conventional approaches at different organizational research levels have emerged and, thus, AI associated with gene and cell therapies could supplant conventional pharmacotherapy and facilitate the diagnosis of pathologies. Using the examples of chronic pain and neuropathic disorders, which affect a large number of patients, I illustrate here how AI could generate new therapeutic approaches, why some compounds are seen as recreational drugs and others as medicinal drugs, and why, in some countries, psychedelic drugs are considered as potential therapeutic drugs but not in others.

Introduction

Scientists, social scientists, and humanists must communicate with and understand each other because the survival of human-kind requires the development of scientific programs the social implications and human consequences of which have to be taken into account. Regardless of the applications of their discoveries, scientists in general and medicinal chemists in particular as creators of new molecules, should always recall the wisdom of Indian Iroquois tribes: before taking a decision that could have consequences for the future of the tribe, Iroquois chiefs evoked the impact that this decision would have had on seven past Iroquois generations [1]. Today, although new technology inventors think about the impact of their discovery on future human generations, most do not consider the negative impact they might have had on past generations. This statement holds true for the discovery of new molecules regardless of their fields of application, be it health, agriculture, or advanced materials for industrial purposes, among others. Thus, wisdom should be the

prime quality of chemists creating new molecules, who should never forget that molecules at the origin of life on Earth are at the base of the current pharmacopeia used by humans. Small molecules of life at the basis of the world pharmacopeia Starting from organic molecules derived from carbon and other elements, such as hydrogen, oxygen, sulfur, and nitrogen, millions of combinations exist in nature or have been synthesized, including those upon which life itself is based. The most significant are the molecules that constitute the code of life, which have revolutionized our understanding of biological phenomena. Nature has equipped every cell with a complete set of blueprints stored in the nucleus in the form of molecules of DNA, involved in genetics and protein synthesis [2]. Then come the so-called 'molecules of mercy', namely pain relievers. The most popular is perhaps acetyl salicylic acid (aspirin), medicinally used to alleviate common aches and pain. Many of the established organic molecule-based pain relievers occur naturally in plants, with morphine, which is 50 times as potent as aspirin, a notable example. Related to the morphine family, numerous structurally related analogs and other drugs, such as heroin, methadone, codeine, pentazocine, cocaine, procaine, atropine, and scopolamine, have been described. Sometimes addictive, sometimes sedative, such drugs, including barbiturates and tranquilizers, have their place in medicine if used correctly [3]. The fundamental problem related to such drugs is that they are open to abuse. Feel tense? Take a pill. Can't sleep? Take a pill. How many times do we hear such refrains? Humans take energizers, sedatives, analgesics, and even hypnotics to better cope with their pressure-filled lives. Even Cleopatra supposedly took sleeping pills while Mark Anthony was away on a trip! Medicinal chemists have synthesized specific drugs to satisfy increasingly pressing demands from society, resulting in compounds such as barbiturates and tranquilizers (e.g., phenothiazine, meprobamate or chlordiazepoxide). Unfortunately, drug-taking by itself is rarely a cure for psychological conditions, and some of these drugs can be dangerous if used without proper guidance. In addition to drugs for pain and psychological conditions, humans have also exploited naturally occurring compounds to create specific molecules to treat microbial disease. For example, quinine and other antimalarials, sulfanilamide, penicillin, streptomycin, chloramphenicol, and tetracyclines were developed against resistant strains of microorganisms. However, given the prevalence of multidrug-resistant organisms, there is a continuing need to create and synthesize new antibiotics to control such organisms [4]. The steroid family and related compounds represent a major breakthrough for medicinal

chemistry development, because these compounds have various important biological functions, including as vitamins, sex hormones (testosterone, estradiol, and progesterone), contraceptives (norethindrone) and arteriosclerotics (cholesterol), which represent major areas of steroid involvement [5]. Another family of compounds with diverse hormone-like effects are prostaglandins, found in almost every tissue in humans and other animals, and which have a variety of effects, including as vasodilators, in platelet aggregation, inflammation, or smooth muscle contraction [6]. Our unending search for life's meaning, deep psychological satisfaction, and insights into immortality have led us to collect, catalog, and even concoct substances that allow us to transcend normal physical limitations and routines. This is why humans have been interested in so-called 'molecules of mysticism': the mind changers [7]. Humans have eaten, imbibed, sniffed, and inject extracts of plant and animal origin to achieve altered consciousness. Four classes of molecule that affect mental processes can be distinguished. Most fit into the classification of hallucinogenic or psychomimetic drugs, or significant mind-altering molecules: (i) lysergic acid derivatives (LSD, alkaloids from *ololiuqui*, etc.); (ii) phenethylamine compounds (mescaline, amphetamines, etc.); (iii) tryptamine-based molecules (psilocin, psilocybin, bufotenine, etc.); and (iv) cannabinoids from *Cannabis sativa* (hashish, marijuana, etc.).

The suggestion that doctors should be paid for keeping people healthy, rather than curing them after they get sick, has been at the origin of the growing interest in vitamins and in so-called 'health foods'. It is also why medicinal chemists have been involved in the creation, synthesis, and biological studies of molecules of growth and health. These molecules are mainly vitamins [8], discovered primarily by scientists seeking to cure specific diseases, such as beriberi, facial tissue deterioration and related forms of dermatitis, pellagra, scurvy, and night blindness, which all arise from vitamin deficiencies, mainly vitamin B1 (thiamine), vitamin B2 (riboflavin), vitamin B6 (pyridoxine), nicotinic acid (niacin) and nicotinamide, vitamin C (ascorbic acid), vitamin A (retinol), and vitamin E (tocopherols). The structure and chemistry of these molecules of growth and health differ substantially from each other, but have important role as cofactors in regulating appropriate enzyme actions. Who among us cannot recall the effect of head colds or simply blocked nasal passages on our sense of taste? Thus, molecules of the senses (taste, odor, and attraction) have been isolated and synthesized by chemists: (i) taste molecules: monosaccharides (glucose and related analogs), disaccharides (maltose and lactose), amino acids and peptides that have a sweet taste.; (ii) odor molecules, which

can belong to different types of fragrance: camphoraceous, (D-camphor); pungent, (formaldehyde, acetic acid, allyl alcohol); ethereal, (chloroform, propyl alcohol), floral, (geraniol, terpineol, ionones, benzyl acetate); peppermint (menthone, cyclohexanone, piperitol), musky (cyclohexadecanone, androstanol, muscone); and putrid (cadaverine, skatole, amymercaptan, hydrogen sulfide); and (iii) molecules of attraction (pheromones), which are chemical substances that allow intraspecies communication. The structure and chemistry attraction pheromones, such as disparlure and propylure, differ substantially from each other depending on the species. The common denominator among these molecules is that they are volatile, long-lasting, and have a potential irritating quality. Terpenoids and related molecules are common types of molecule isolated from insects and ants and which are used in defense, such as citronellal, geraniol, citral, farnesal, limonene, and perillene. Benzoquinones and related analogs are among the most widely distributed arthropod defensive compounds. Other compounds, such as cresols, salicylaldehyde, benzoic acids, and benzaldehyde, have also been isolated. Synthetic organic chemists have focused on insect pheromones with the aim of controlling the destructive feature of insect populations. Numerous attractants and repellents have been discovered, such as trimedure against Mediterranean fruit flies, methyl benzoate against mites, N-butylacetanilide against ticks, and 2-butyl-2-ethyl-1,3-propane diol against mosquitos. Although such compounds were designed to be effective, safe, and specific for the particular species, some are ineffective and can even be toxic. Given the earlier discussion of our exploitation of naturally occurring molecules, the resulting large numbers of approved pharmaceutical medicines worldwide, and the fact that their effects are sometimes suboptimal, would it now be better to search for new health treatments using gene or cellular therapies rather than to continue the research and development of small molecules? Most traditional drugs, as well as >90% of therapeutics currently marketed, are small molecules [9]. The key drawbacks of conventional small-molecule therapeutics are that they can do only one thing and that they keep doing it, regardless of the physiological state of the patient, because they are not equipped to receive feedback from the body. One significant example are beta-blocker drugs, which keep blocking the functioning of the heart regardless of the physiological state of the patient [10]. One area where small molecules are, and will likely remain, the best possible therapeutic tools, is the fight against bacteria, fungi, and viruses. Small-molecule inhibitors are effective antimicrobials because they target enzymes specific to the target

species. However, when our own proteins need to be regulated for therapeutic purposes, the 'single-mindedness' of enzyme inhibitors or receptor ligands, as well as their unresponsiveness to signals sent by the body, remain problematic. This is why new immunological or genomic therapies are emerging and beginning to replace existing standard small-molecule drugs.

New therapeutic cellular approaches: the use of large molecules

Cellular behaviors, such as adhesion, migration, and cell death by apoptosis or other mechanisms, are mediated and regulated via protein–protein interactions (PPIs). The ability to selectively disrupt or enhance individual PPIs gives unprecedented leverage over the cell, essentially telling the cell what to do, and when to do it, in a language that it understands [11]. This could help to elucidate the intricacies of cell signaling, which is currently a significant challenge in biological research. By introducing a protein with modified signaling properties into a cell, it is possible to affect the behavior of that cell. Cancer cells and dying neurons represent obvious targets. Given that the biological function of signaling proteins is to deliver chemical messages, if one could tell cancer cells to stop proliferating and dying neurons to stay alive, crucial disease could be cured or prevented. Viral and non viral gene delivery systems, as well as the identification of promoters driving expression in specific cell types, are under development [12]. A recent application of such a technique was the treatment of Leber congenital amaurosis (LCA), a rare inherited eye disease that appears at birth or during the first few months of life; using adeno-associated virus gene therapy, it was possible to restore vision in patients with LCA [13]. For therapeutic purposes, it is often necessary to selectively enhance or reduce only one interaction with a particular signaling protein, out of several that are normally engaged in the target reaction. Arrestins, a small family of proteins, important for regulating signal transduction at G-protein-coupled receptors, represent a significant model for specific interaction approaches, because these elongated molecules have a variety of roles in several biological processes, such as the regulation and localization of phosphodiesterase, programmed cell death, infectious diseases, host–pathogen interactions, regulation of GTPases, airway epithelium and asthma, as well as pain and anesthesia [14]. Arrestin binding to a receptor blocks further G protein-mediated signaling, targets receptors for internalization, and redirects signaling to alternative G protein-independent pathways [15].

Drugs for medical use: the therapeutic context

The search continues for new drugs or molecules with improved biological properties, which ideally would only have beneficial health benefits. To address this challenge, several questions arise, such as: (i) in what therapeutic context can drugs be used and in what form? (ii) How can we measure the benefit–risk ratio of the medical use of drugs? (iii) How can we supervise the production and sale of drugs for medical use? (iv) What is the difference between a drug and a medicinal drug? (v) Why are certain molecules for recreational use struck by pharmacological infamy? Let us consider first the case of psychoactive drugs. Thirty countries have legalized cannabis for therapeutic use. France remains resistant to the commercialization of treatments involving cannabinoid derivatives for certain forms of epilepsy, multiple sclerosis, or chronic pain. However, behind the possible use of cannabinoids, there is a whole family of molecules that are beginning to be researched and used for such conditions, the so-called ‘molecules of mysticism’ or ‘mind changers’ [16]. Can we legalize those drugs for medical use? Questions about their use, the lack of legislation, and reluctance around their therapeutic application, too often considered as recreational, are still questions that need to be addressed, because some of these compounds could be helpful for patients with chronic pain, spasms (notably linked to multiple sclerosis), or certain childhood epilepsies. Hallucinogens and psychedelic drugs are being investigated to discover possible new therapeutic applications. Researchers are studying the action of hallucinogenics on certain treatment-resistant pathologies, such as chronic depression, alcohol and drug dependence, post-traumatic stress disorder, and obsessive-compulsive disorder (OCD). In France and other countries, some psychedelic drugs are illegal, such as ketamine, LSD, MDMA (ecstasy), psilocybin mushrooms, ayahuasca, and ibogaine [17]. Such compounds, similar to chemotherapeutic drugs for cancer, or morphine for pain, would need to be administered cautiously. Although such psychedelic drugs are listed as illegal because they alter states of consciousness, they could be also interesting as medical treatments. As an example, A. Huxley took mescaline, the active alkaloid of peyote, the Indian cactus, resulting in colorful visions accompanied by various psychological phenomena [18]. However, the use of hallucinogens and narcotics as ‘anti-intellectual’ drugs would be an inappropriate way to find answers for medical conditions currently lacking effective treatments [19,20]. A recent study reported that psilocybin was effective at reducing symptoms in humans with treatment-resistant depression [21]. Psilocybin can help patients become more optimistic and could be an effective way to

treat tobacco [22] and alcohol abuse [23]. Patients who used psychedelics have lower rates of psychological distress and suicidality compared with those who do not use psychedelics; for example, psilocybin made patients living with lung cancer more comfortable compared with control groups [20]. Even if results from clinical trials with psilocybin were promising, psychotherapy trials confirming its efficacy and safety are still needed.

Nevertheless, the potential effects of psilocybin on depression, anxiety, and palliative care should be considered in future studies.

The case of drugs for chronic pain

Research is beginning to focus on searching for new synthetic molecules and new immunopharmacological approaches to replace conventional drug therapies. The development of therapies for chronic pain is an example of research duality between new synthetic molecules (small molecules) and immunological approaches involving large molecules (proteins, chemokines, and neurokinins). Chronic pain is a major problem for human health, affecting 20% of the world's population; it also has a considerable economic impact and its impact will continue to increase with increasing life expectancy; in addition, chronic pain is the number one cause of long-term disability in the USA; 27% of chronic pain is related to low back pain; 77% of patients with chronic pain report feeling depressed because of their condition; and 66% of patients seek treatment from medical doctors, 25% from chiropractors, and 15% from pain specialists [1]. Opioids continue to be prescribed to patients with chronic pain despite the fact that their use is broadly accepted to be most effective for acute pain, cancer pain, and palliative care. Additionally, only 23% of patients with chronic pain found opioids to be effective [24]. Chronic and neuropathic pain treatments mainly rely on chemotherapeutic agents. Chronic (nociceptive) pain from tissue inflammation or damage (as in rheumatoid arthritis and cancer pain) is best treated with opioids, such as opiophin [25], whereas neuropathic pain (caused by a damaged or dysfunctional nervous system) is treated more effectively by drugs such as tricyclic antidepressants [26], serotonin-norepinephrine reuptake inhibitors, and anticonvulsants [27,28]. For example, lacosamide [a US Food and Drug Administration (FDA)-approved drug] abolishes the disease-specific phenotype by blocking induced pluripotent stem cell (iPSC)-derived nociceptors [29].

Unfortunately, the use of most standard chemical synthetic drugs, including paracetamol-like drugs, acetyl salicylic analogs, noramidopyrine, floctafenin, nefopam, codeine derivatives, and other potent analgesic drugs, including morphine-related analogs, often induce adverse

effects; thus, new immunological treatment approaches are under investigation. One such approach reported was the injection of a chemokine-like protein TFAFA4, in animal models of inflammatory or nerve injury-induced pain. TFAFA4, a chemokine-like protein, was shown to modulate injury-induced mechanical and chemical pain hypersensitivity in mice [30]. Another approach was based on the development of molecular-specific sodium channel (NAV 1.7, NAV 1.8) blockers [31,32]. Natural toxins, such as saxitoxin [33] and aryl sulfonamide [34], show promise for treatment of neuropathic pain with minimal adverse effects.

Role of AI in the development of new drugs and diagnostics for chronic pain and neuropathic disorders

The use of AI in the health sector research has considerably modified conventional approaches at different levels in the drug discovery process. Design, synthesis, identification, and screening of new therapeutic molecules. The synthesis of molecules remains one of the most important challenges for organic and medicinal chemists. Performing algorithms, such as the Chematica Computer Program [35], has shown the effectiveness of AI in providing chemists with realistic solutions for molecule synthesis. For several decades, software allowing predictive structural drug and protein determination have been available, such as predictive nuclear magnetic resonance (NMR), and mass spectrometry (MS)/liquid chromatography (LC) software [36]. Some software provides support for developing molecular models de novo, whereas others directly support aspects related to constructing molecular models, including molecular graphics, interactive drawing and conformational editing. Such software is now frequently used by medicinal chemists and structural biologists [37]. Using AI techniques with robot algorithms enables researchers to quickly conduct millions of chemical, genetic, and pharmacological tests to rapidly identify active compounds, antibodies, or genes that modulate a particular pathway; such high-throughput screening is increasingly the technology of choice in drug discovery and is relevant to both the biology and chemistry fields [38].

AI in medicinal biology, diagnostic assistance programs, and personalized patient treatment programs

The 'omics revolution requiring Big Data mining has been the major driving force behind the development of AI. The first comprehensive systems-biology dynamical model explaining patterning in planarian regeneration provided an automated, highly generalizable framework for identifying the underlying control mechanisms responsible for the dynamic

regulation of growth and form [39]. Such systems could be helpful for clinical research in regenerative medicine. The first aim of health-related AI applications is to analyze relationships between prevention or treatment techniques and patient outcomes. Various specialties have shown increased use of AI to this end, such as disease diagnosis using computed tomography (CT), and magnetic resonance imaging (MRI) techniques [40]; deep learning algorithms have been developed to search reports and detect patterns that imply drug–drug interactions [41]; skin cancer was detected more accurately using an AI system that used a deep learning convolutional neural network compared with dermatologist-based assessments [42]; and in radiology, an algorithm was created that could better detect pneumonia in patients [43,44]. The ability to monitor patients using AI could allow for direct communication to physicians in terms of whether possible disease activity might have occurred [45]. In addition, an AI tool that scans electronic health record (EHR) data can accurately predict the course of disease in a person [46]. The primary aim of health-related AI applications is to analyze relationships between prevention or treatment techniques and patient outcomes. Among these applications, personalized medicine, and patient monitoring and care represent the major challenges to be addressed [47]. AI application for the development of treatment protocols, such as treatment–biomarker combinations in colon cancer (Erlotinib–EGFR) and lung cancer (Crizotinib–ALK), good examples of personalized treatments [48]. Other successful example of AI application is the prediction of correct personalized dosing treatments. AI applications in chronic pain Technologies to accurately evaluate a patient’s pain level are necessary given that half of patients with chronic pain also experience anxiety or depression at some point because of their pain. Difficulties arise when carers try to ascertain a patient’s pain levels, because sensations are inherently hard for patients to express. However, different AI options are available for this purpose: The My Intelligent Assistant (MIA) software was developed by a French start-up Santé Net (www.mia-software.com) incorporated in a bot. It regularly asks patients with chronic pain questions about their pain intensity, fatigue, and how frequently they are taking medication. This allows patients to spontaneously note pain as it occurs, relaying the information to their carer and keeping them informed. It also allows medical professionals to clearly identify when a patient needs to take a sleeping pill. This also helps to combat the over-reliance on powerful and highly addictive analgesics, such as morphine. This algorithm also allows

Patients to manage their pain autonomously with personalized therapeutic advice based on the data that they provide. AI can be used to assess pain levels through facial recognition technology, which notes movements such as furrowed eyebrows, squeezed lips, and raised cheeks, to calculate pain levels. This technology can also be used by anesthetists when determining the dose of morphine required for a patient. However, such technology is only used for treating sharp, short-lasting pain. For patients who endure pain for a long time, the body alarm system stops working in a way which cannot be monitored by such technology. AI can also be applied to neuropathic pain measurement based on brain imaging. For example, brain images from individual patients with chronic low back pain were collected when their pain was at a low (baseline) state. The patients then performed physical maneuvers intended to temporarily increase their pain, including movements such as sit-ups and back-arching motions, and then underwent repeated imaging. By using a machine-learning (ML) approach to compare brain images from individual patients in the two states, researchers identified other specific brain areas that were activated by exacerbated pain; by contrast, in normal pain, brain activity was increased only in the thalamus, a sensory-processing station in the brain [49]. AI can also be exploited as an imaging biomarker for clinical pain measurement. A specific biomarker that could be used for diagnostic purposes to prove whether someone has chronic pain would be of value [50]. Although in the early stages of development, methods including structural and functional MRI and electroencephalography, are being used. These methodologies have already produced encouraging predictive models that have been tested on clinical populations [51].

AI applications in neuropathic disorders

Disruptive technologies, such as ML algorithms, are especially relevant to the discovery of compounds targeting neuropsychiatric disorders, in which current therapies lead to many off-target effects. Leveraging AI technologies, new molecules are being derived from psychoactive small-molecule compounds (SMC), such as psilocybin or LSD, to tackle unmet medical needs in mental healthcare. The development of sophisticated ML algorithms provides a set of tools that can improve discovery and decision-making for specific questions based on sufficient, high-quality data. A typical application of SMC technology is psilocybin therapy [19], which aims to develop compounds with the therapeutic benefits of psilocybin for depression, but with improved characteristics, such as quicker drug release and absorption or the absence of hallucinogenic effects typical of psychedelics. These technologies do

not aim to replace classical psychedelics completely. Instead, the reformulation of psychoactive seed SMCs endeavors to make psychedelic therapy more accessible to a larger proportion of the population, such as those who react unfavorably to the hallucinatory effects or those individuals with cardiac problems

.Concluding remarks

‘Nature invents and man tries to copy it’. From the formation and evolution of initial molecules that gave rise to families of increasingly complex natural molecules with extraordinary biological properties, organic chemists in general and medicinal chemists in particular, have never stopped trying to create molecular structures with improved biological properties for use in the clinic. To achieve this, research chemists have teamed up with biologists, doctors, physicists, and mathematicians to respond as effectively as possible to the major challenges of keeping humans healthy. Technologies offered by AI have been used at all levels of research, from the development of new methods of synthesis to methods of application leading to personalized medicine. Although such approaches are likely to lead to exciting developments in human healthcare, they are likely to come at a cost, and it is currently unclear whether all those who would benefit from them will be able to afford to do so.

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