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Addiction, Experimental Models and Neurobiological Mechanisms

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Abstract – Humans have constantly sought to alleviate their existential anxieties, first resorting to substances found in their natural environment, and more recently, with the arrival of modern chemistry, using synthetic substances or medications. The substances used in this way are constantly renewing, warranting health surveillance and particular vigilance towards the addictive risk, given its major medical and social impact. This surveillance and vigilance requires detailed, accurate knowledge of the pharmacological and physio-pathological models involved in the emergence of the process of addiction, in particular disturbances of the systems regulating dopaminergic transfer; it also requires knowledge of the means to identify individual risk factors linked to genetic or psycho-behavioural susceptibilities.

Abbreviations: see end of article.

1. Introduction

Since time began, humans have sought the means to alleviate their existential anxieties, first using substances found in the natural environment, and more recently, with the arrival of modern chemistry, using synthetic substances or medications. The use of these substances procures pleasurable feelings *via* the activation of the reward circuit, where the main agent is dopamine. While this usage is at the outset most often recreational, or indeed therapeutic, this purpose is sometimes overtaken, and the subject becomes dependant on the substance involved, experiencing physical and mental pain in case of abstinence, craving, and an irrepressible desire to resume its use. The ephemeral pleasure derived from substance use is gradually replaced by the sole need to have it, with social and medical consequences that mean suffering for the subject and those around him or her.[1,3] The substances that are used or misused are constantly renewing, which requires health surveillance measures, in particular towards the risk of addiction. This surveillance and monitoring requires detailed knowledge of the physio-pathological mechanisms, of models of the dependency process, and of the means to detect addiction risk.

2. Addiction: from natural substances to synthetic psychotropics

Humans soon found the means in their natural environment to alter their brain functioning and induce affective, emotional and cognitive effects generating feelings of pleasure, thus relieving or obliterating existential human suffering. There are numerous examples of this quest: cannabis, bethel nuts, hallucinogenic mushrooms, coca leaves, cape gooseberries, poppy flowers and others.[4,5] When nature alone no longer sufficed, people began to modify these substances to obtain substances with psychotropic properties. The best example of this is alcohol, the first instance of the impact of a chemical alteration, here by way of fermentation. It was however only after the development of extraction processes in the 18th century that the active substances responsible for psychotropic effects were progressively identified. The identification of the relevant molecules made the mechanisms involved easier to apprehend, so that there was a shift from a rather mystic view of these substances, as in Baudelaire's phrase "artificial paradises", to a more scientific view which opened the way to neuro-psycho-pharmacology.[6] Naturally, the improving knowledge of the mechanisms of action of the "natural" psychotropics opened

the way to synthetic psychoactive drugs, where the purpose was initially therapeutic, but the usage of these substances was then diverted towards illicit usage, or uses for which the drugs were not initially intended.

Different preparations based on morphine were used, for pain control purposes or to sedate agitated patients, in oral form and later in injectable form. The search for new cough medicines based on morphine, rapidly known for its respiratory depression effects, led to the synthesis of diacetylmorphine, referred to as a "heroic" drug by its developer. Thus heroin was born, marketed in 1898 as a cough medicine, but its strong addictive properties soon led to usage that was primarily illicit rather than therapeutic.[7] Amphetamines are linked to the development of bronchodilators such as ephedrine, the psycho-stimulant properties of which were very soon recognised. This led to numerous other amphetamine-based substances, the most recent of which is methylenedioxymethamphetamine (MDMA) or ecstasy.[8,9] The history of tranquillizers is closely linked to their muscle-relaxant effect. It was indeed when looking for antibiotics that Franck Berger came upon mephenesin because he noticed its muscle-relaxant effect on laboratory mice.[10] A substance derived from mephenesin, meprobamate(Equanil®) was the first tranquillizer marketed in 1955, but it was rapidly rivalled by the benzodiazepines, the first of which, chlordiazepoxide (Librium®) was developed in 1958 by Leo Sternbach.[11] It was from the structure of a phenothiazine, which produced chlorpromazine, the first antipsychotic, and imipramine, the first antidepressant, that chlordiazepoxide was developed. Its metabolite, diazepam (Valium®) was for some years the world leader in tranquillizers following its marketing in 1963. The anxiolytic effect rapidly took precedence over it mere muscle-relaxant effect, which explains the popularity of this class of psychotropics and its over-prescription. Other substances, such as lysergic acid diethylamide (LSD) or phencyclidine, were substances that were specifically aimed at "recreational" use, and were the not subject to pharmaco-therapeutic development.

If we consider the effects of these different substances, it becomes obvious that the boundary between recreational usage and risk of addiction is not clear-cut. Indeed, it is the recreational aspect, the sensation of pleasure or the reduction of anxiety, rather than dependency, that are sought after by users. Nevertheless the neurobiological effect on the reward system, often not the main mechanisms of action, coupled with repeated usage are what lead to deregulation of the motivation and reward circuits, inhibiting control, and memorisation which underpin dependency and addiction.[12] Different models, whether pharmacological, experimental or neurobiological, give insight into the shift from recreational use to loss of control and compulsive use, the main characteristics of dependency and addiction. Addiction also needs to be envisaged at individual level *via* a model of interaction between genetic susceptibility and psycho-behavioural vulnerability, and at collective level *via* the modelling of its social impact.

3. Addiction: the pharmacological model

Progress in the field of neuro-psycho-pharmacology and in molecular biology has in the space of a few decades made it possible to characterise the cellular and molecular targets of psychotropic substances, whether therapeutic or illicit.[13–15] The receptor targets and their regional or cellular locations are numerous, and explain the diversity of the pharmacodynamic effects produced. Certain substances act through neurone activator systems, thus explaining i) psychostimulant effects (psycho-motor excitation) in particular *via* the activation of the mono-aminergic systems by increasing their release (amphetamines, methylphenidate, ecstasy), or by inhibition of their reuptake (cocaine, antidepressants), or *via* the cholinergic system and its nicotine receptors; ii) psychodysleptic effects, through interaction with certain subtypes of glutamate receptors (phencyclidine), with cannabinoid receptors (cannabis), and with certain subtypes of serotoninergic receptors (LSD, mescaline). In contrast, other substances act on systems that are inhibitors of neurone activity, explaining their anxiolytic effect and the corollary de-inhibition effect. This is the case with alcohol, barbiturates, or benzodiazepines, which act *via* a receptor complex that is sensitive to gamma-aminobutyric acid (GABA). The modulation of opioid receptors by opiates (morphine and derived substances, heroin) produces both positive effects such as feelings of well-being and euphoria, sometimes bordering on something resembling an orgasm, and pain-inhibiting effects which also contribute to the hedonic effect.

While the main mechanisms of all these addictive substances are diverse, the existence of hedonic properties that are fairly similar and lead to repeated use in order to retrieve the sensations suggests a possible shared final pathway. Experiments in primates and rodents have enabled the identification of reward circuits which, when stimulated, produce pleasure, driving the animal to seek to return to the circumstances in which this brain system is electrically activated.[12,16] This ability to reinforce the activation of the reward system is also procured by natural or synthetic substances, which explains repeated use of the substance to retrieve the pleasure reinforcement effect. In this paradigm, the notion of pleasure includes both the emotional aspect (the hedonic sensation) and the motivational aspect (the activity of sensation-seeking) [figure 1]. From an anatomo-functional viewpoint, this reward circuit is located in the ventral tegmental area, which is a small zone situated in the upper brainstem close to the substantia nigra controlling movement. Its neurones project towards the nucleus accumbens, a striatum zone linked to the limbic system and