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Review Article

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Baclofen® as anti–craving agent against several addiction

Abstract

The surge in dopamine in ventral striatal regions in response to drugs of abuse and drug–associated stimuli is a final common pathway of addiction processes. $GABA_B$ agonists exert their effects indirectly, by quieting dopaminergic afferents. The ability of the $GABA_B$ agonist, baclofen® to ameliorate nicotine and drug motivated behaviour, particularly with respect to its possible utility as a smoking cessation agent. This article provides a review of the use of baclofen® in the treatment for different addiction. First, we present a brief overview of treatments of addictions for various substances of abuse, including alcohol, nicotine, and cocaine. Second part, summarizes the state of knowledge about the chemistry and toxicology of cigarette smoke. The section on "Chemistry" describes the chemical components of cigarette smoke and addresses aspects of product design. Finally, we come back to discuss some problems related to properties of baclofen® that needs to be resolved, and our current investigation, to improve the therapeutic activity of baclofen®. We conclude by an open question to doctors (addictologists and psychiatrists) hoping an answer as soon as possible.

Keywords: baclofen®, addiction, tobacco, alcoholism, synthesis analogs

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Abbreviations: ANSM: Agence National de Sécurité du Médicament; VTA: Ventral Tegmental Area; Acetylcholine: Acetylcholine; NNK: Nicotine–Derived Nitrosamine Ketone; NNN: Nitrosonornicotine; CDs: Cyclodextrin; DGRS–DT: General Directorate for Scientific Research and Technological Development

Introduction

Baclofen® is an old drug marketed for over 40 years. It is used as antispastic agent and muscle relaxant.[1] Therefore, we know the side effects and have a good perspective on prescription (Figure 1). In 2004, the French doctor Olivier Ameisen, desperate to cure his addiction to alcohol, tests baclofen® on itself and finds at high doses, it removes the urge to drink "anti–craving". The release of the book "The end of my addiction".[2] baclofen® is mediated, and presented as a new alternative in the treatment of alcoholism and the other addiction. The use of baclofen® as anti– craving agent, received on 14 March 2014, a temporary recommendation from ANSM (Agence National de Sécurité du Médicament) for use in treatments of several dependences.

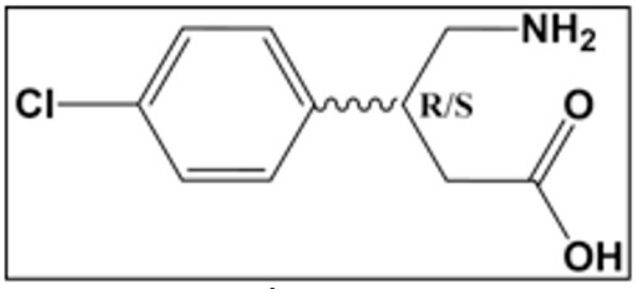

Figure 1 Chemical structure of baclofen®.

Addiction mechanism: treatment and use of baclofen®

Cigarette dependence is the most common form of chemical dependence in the nation and is as addictive as heroin, cocaine, or alcohol.[3] The list of debilitating and/or fatal diseases that are worsened by or attributed to cigarette smoking continues to grow (Foundation for smoke–free America.[4]) Quitting greatly reduces the risk of premature death related to lung and other types of cancer, coronary heart disease, stroke and numerous other illnesses (The Health Benefits of Smoking Cessation. A Report of the Surgeon General, 1990). However, quitting is not easily accomplished – 70% of smokers want to quit each year but less than 7% succeed.[5,6]

Based on consistent preclinical studies over the last 30 years it is believed that the dopamine surge in the ventral striatum in response to addictive drugs and stimuli (cues) previously and repeatedly 'paired' with the drug leads to drug–motivated behaviors.[7–9] Similar findings are now being replicated in humans. At least two studies reported that cocaine cues elicit craving and increased dopamine release in the striatum of cocaine addicted individuals.[11,12] Boileau and colleagues showed that three administrations of amphetamine within the same environment produced conditioned dopamine release in the ventral striatum accompanied by amphetamine–like behavioral responses.[13] Further support for the role of dopamine is provided by Franklin and colleagues wherein both brain and behavioral responses to smoking cues were modulated by genetic variance in the dopamine transporter.[14] a key component regulating the dopamine system.[15]

It is theorized that GABA–ergic agents reduce dopamine availability in the ventral striatum.[16,17] thereby preventing the self–administration of psychoactive drugs.[16,18] These effects are reversed by GABAB antagonists demonstrating specificity.[19,20] The mechanisms are still under investigation but one hypothesis is that activation of GABAB receptors located somato–dendritically on ventral tegmental area (VTA) neurons inhibit the release of dopamine in interconnected regions such as the ventral striatum and prefrontal cortex.[9,19,21]

It is well established in the animal literature that the GABAB agonist, baclofen® is effective at reducing dopamine release and in reducing drug–seeking motivated behavior at doses that do not affect responding for food, water, or locomotor activity.[20,22–28] Other investigation done by Fattore and colleagues reported that baclofen® dose– dependently blocked nicotine–induced reinstatement of self–administration in rats and dose–dependently abolished nicotine conditioned place preference in mice.[29]

Although studied much less in clinical settings, the results are consistent with the animal literature showing that baclofen® treatment reduces motivation to use addictive drugs. Baclofen® reduced drug use and craving in cocaine.[30,31] amphetamine.[32] and alcohol.[33–36] dependent individuals.[37] In a study examining the effects of baclofen® on opiate dependent subjects, baclofen® significantly increased treatment retention, decreased withdrawal symptoms, and showed a trend in reducing craving.[38] Three case studies in alcoholics report complete remission as indexed by the absence of craving and alcohol use.[39–41] A laboratory study conducted by Cousins and colleagues examined the effects of a single dose of baclofen® on subjective effects of smoking in non–treatment seeking smokers. Baclofen® negatively impacted cigarette enjoyment and increased feelings of relaxation, both of which may facilitate eventual abstinence and aid in relapse prevention.[42] To our knowledge, there are no published studies examining the effects of baclofen® treatment (chronic dosing) on smoking behavior.

Baclofen® is an FDA–approved GABAB agonist used for the treatment of spasticity since the early seventies.[43–45] It does not carry a significant abuse liability.[33] it is self administered only minimally by rhesus monkeys or baboons.[46,47] and other than initial mild sedation, has few side effects.[48] Its safety and tolerability has been confirmed in numerous studies over the years, including studies in alcoholics and cocaine addicts.[34,36,45,49,50]

Based on the pre–clinical and clinical evidence summarized above, we can say that baclofen® is being used more frequently for treatment of different addiction; alcohol, tobacco and many other substances (cocaine, heroines.), but physicians and psychiatrists should be on the watch for a possible increase in number of cases of baclofen® overdose.

Smoking chemically

Addiction of nicotine

Mortality among current smokers is 2 to 3 times as high as that among persons who never smoked. Most of this excess mortality is believed to be explained by 21 common diseases that have been formally established as caused by cigarette smoking.[51]

That smoking causes cancer is a well-known and scientifically proven fact. Everyone knows that nicotine is present in cigarettes, and causes addiction to smoking; however, what's a little less well known is the range of chemicals contained within cigarette smoke that can lead to carcinogenic (cancer causing) effects, and what other effects they can have on the body. The effects of some of these chemicals also explain why it's advised that women shouldn't smoke during pregnancy (Figure 2).

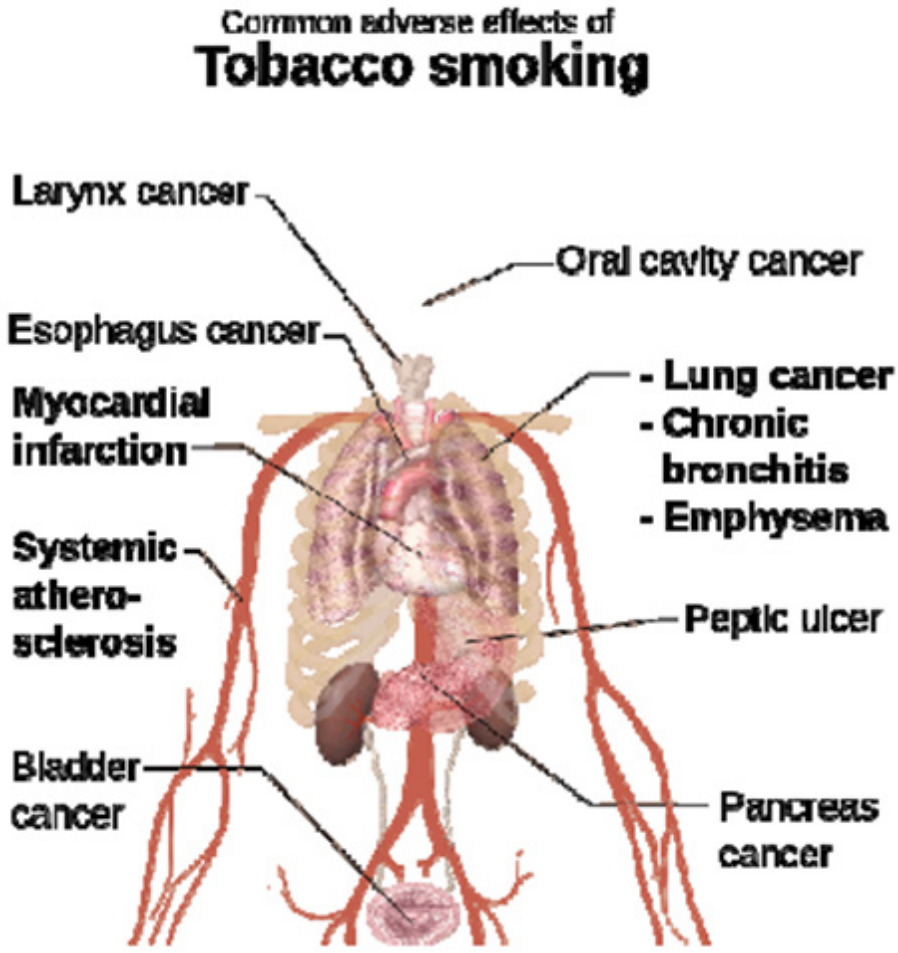

Figure 2 The effects of cigarette smoking to human health.

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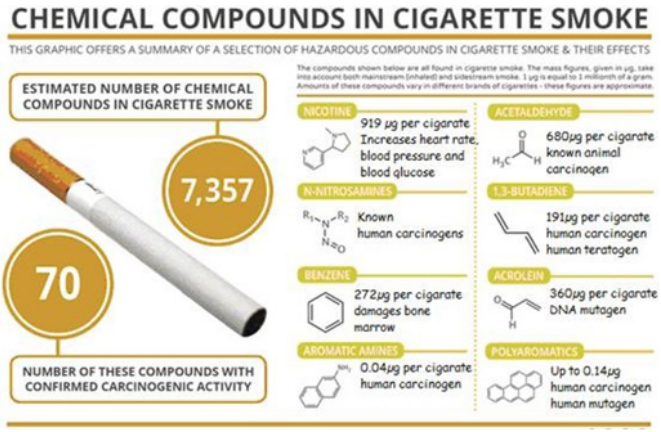
Cigarette smoke contains a huge number and range of organic compounds. Estimates in the past few years state that there are almost 7360 different compounds present, and it is likely that this number could still increase. Of this massive number of compounds, 70 have confirmed carcinogenic activity in humans, and many more are suspected carcinogens.

Let's start with an obvious chemical first, however: the non–carcinogenic nicotine. Nicotine is a member of the alkaloid family of compounds, a family of which caffeine is also a member. Cigarettes contain, on average, around 10mg of nicotine; when it is inhaled in cigarette smoke, it is absorbed into the bloodstream, and when it reaches the brain it stimulates the production of a number of neurotransmitters. Nicotine impersonates the neurotransmitter acetylcholine (ACh), and by binding to receptors ACh would usually bind to, stimulates the production of dopamine, which is involved in your body's 'reward' pathways. This leads to the addictiveness of smoking.



Let's take a look at some of the other organic compounds in cigarette smoke with more harmful effects:

N–nitrosamines

These are a large class of nitrogen–containing organic compounds. The majority of nitrosamines that have been studied have been shown to cause DNA mutations, and several are known human carcinogens, including some that are specific to tobacco. Of these, NNK (nicotine–derived nitrosamine ketone) and NNN (nitrosonornicotine) are considered to have the highest risk for carcinogenic action. Research has shown that the amounts of tobacco specific nitrosamines varies widely, and that low tar brands tend to exhibit lower levels of these compounds – though they remain present.[52–54]

Benzene

Benzene is an organic chemical that is actually formed naturally, as a result of occurrences such as forest fires or volcanic eruptions. However, an important source of human exposure to this compound comes from cigarettes, which are estimated to account for up to 50%. Benzene is a proven carcinogen, based on evidence from both animal and human studies. It's also been shown to cause changes to chromosomes in bone marrow under laboratory conditions. Bone marrow is where new blood cells are made, so damage to this can lead to anaemia, and low levels of other blood constituents.[55]

Aromatic amines

Aromatic amines are another family of compounds, often used in the synthesis of pesticides, plastics, and pharmaceuticals. They're also found in cigarette smoke, with their levels tending to be higher in sidestream smoke (that produced at the lit end of the cigarette). Several of these compounds are confirmed human carcinogens, with increasing evidence that they contribute to bladder cancer in smokers in particular.[56]

Formaldehyde & Acetaldehyde

These two compounds are both members of the aldehyde family of compounds. Formaldehyde is known to be a human carcinogen, whilst acetaldehyde is classified as a confirmed carcinogen in animals and a probable carcinogen in humans. Acetaldehyde is in fact the most abundant carcinogen in tobacco smoke, and dissolves into saliva when smoking. Both acetaldehyde and formaldehyde cause irritation of the skin, eyes, throat, mucus membranes, and respiratory tract.[57]

1,3–Butadiene

1,3–butadiene is a simple hydrocarbon molecule, containing 2 double bonds. In a 2003 study.[58] the risk factor of various compounds in cigarette smoke for cancer and heart disease was considered, and 1,3–butadiene presented the highest cancer risk by some margin. It's also a suspected human teratogen (causes deformation of embryos). Studies on animals have shown that breathing butadiene during pregnancy can increase the number of birth defects.

Polyaromatic hydrocarbons

Polyaromatic hydrocarbons are a group of over 100 different organic chemicals formed by incomplete combustion of organic compounds.[59] Several have been identified are carcinogenic, mutagenic, or teratogenic. Benzo–a–pyrene is one of the most potent, and notably was the first chemical carcinogen to be isolated. High exposure to polyaromatic hydrocarbons in the womb has been associated with childhood asthma, as well as adverse post–birth effects including heart malformations and DNA damage.

Baclofen®'s problems: our current investigations

The main problem of baclofen® that is administered as a racemate (Figure1). However, since the R–(–) enantiomer is more active and toxic than the S–(+) enantiomer, the chiral separation of baclofen® in biological fluids is very important in order to achieve an optimal therapeutic response.[60] In addition, the baclofen® is a GABA analog which specifically interacts with the GABAB, which makes it the classic GABA antagonist. But, unlike the latter, the baclofen® can cross (weakly) the blood–brain barrier.[61,62] In view of the disadvantages of the baclofen®, the latter is the subject of several studies, where the main challenge is to optimize bioavailability and vectorization of baclofen®, this by developing methods for separating the two enantiomers and synthesizing new analogs.

The main idea in our synthetic scheme adopted in our work, is the preservation in the target compounds, their two ends, the two free groups, namely the carboxylic acid and free amino. The access to these analogs, from amino acids was the best method compared to other procedures described in the literature.

In order, to get our target analogs of baclofen®, and to improve the properties such as: the bioavailability, the interaction with the GABAB receptor, the reduction of side effects... etc. The therapeutic value and great anti– craving capacity of baclofen®, make it a prime target for our research; our modifications on baclofen®'s structure, are represented on the Figure 3.

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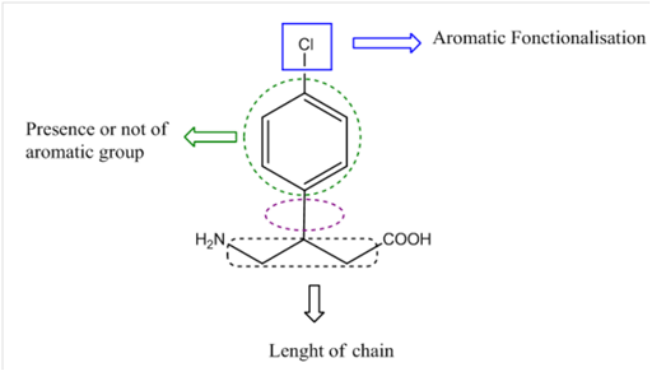

Figure 3 The targets modifications on the structure of baclofene®.

Later, our synthesis analogs are complexed with, native and amphiphilic cyclodextrin (CDs). Our choices is justified by the fact that the formulations with CDs proved to be efficient in providing a way to increase the solubility, the stability and/or other relevant physico–chemical properties of drugs at the same time.[63] We investigated the encapsulation of those synthetic derivatives by (CDs), using different spectroscopic techniques with a view to establishing the stoichiometry of the complexes, calculating the association constant and determining some dynamic aspects of the complexation process.[64]

Conclusion

Tobacco addiction, like many other substances (alcohol, cannabis, cocaine, heroin...), is characterized by intolerable "craving". The urge to smoke is not compatible with abstinence from smoking in the long term which is nevertheless still considered as the best response to tobacco addiction. It follows an irrepressible urge to smoke or consume the substance, the "craving". This is where baclofen® that would block this reward system and thus to eliminate the desire for dependence. The mechanisms are similar to various addictions and still use the dopaminergic pathway, target of baclofen® will indirectly inhibit this pathway by acting on GABAB receptors.

Many tests tend to show some efficacy of baclofen® on tobacco dependence. Dr Renaud de Beaurepaire (thèse Alexandre Dubroeucq, 2011) was the first doctor to prescribe baclofen® for the treatment of smoking and other forms of addiction. The cure of patients was quick and efficient. He also led several doctoral theses and published several articles on the subject, making its results as model references.

Open question

If baclofen® can cure any form of addiction as smoking, alcoholism and other addictions to addictive substances. If it is beneficial effect is already proven, approved, and used as anti– craving agent in several countries in the world. Why until now the Algerian health community does not use baclofen® in treatment of several addiction?

Acknowledgments

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Conflict of interest

The authors declare no conflict of interest.

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