GABA$_B$ receptor as therapeutic target for drug addiction: from baclofen to positive allosteric modulators

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Summary

The present paper summarizes experimental and clinical data indicating the therapeutic potential of the GABA$_B$ receptor agonist, baclofen, in the treatment of alcohol use disorder (AUD) and substance use disorder (SUD). Multiple preclinical studies have demonstrated the ability of baclofen to suppress alcohol drinking (including binge – and relapse-like drinking), oral alcohol self-administration, and intravenous self-administration of cocaine, nicotine, amphetamine, methamphetamine, morphine, and heroin in rodents. Some randomized, controlled trials (RCTs) and case reports support the efficacy of baclofen in suppressing alcohol consumption, craving for alcohol, and alcohol withdrawal symptomatology in alcohol-dependent patients. Data from RCTs and open studies investigating baclofen efficacy on SUD are currently less conclusive. Interest in testing high doses of baclofen in AUD and SUD treatment has recently emerged. Preclinical research has extended the anti-addictive properties of baclofen to positive allosteric modulators of the GABA$_B$ receptor (GABA$_B$ PAMs). In light of their more favourable side effect profile (compared to baclofen), GABA$_B$ PAMs may represent a major step forward in a GABA$_B$ receptor-based pharmacotherapy of AUD and SUD.

Key words: GABA$_B$ receptor; baclofen; positive allosteric modulators, alcohol use disorder (AUD), substance use disorder (SUD), animal models of AUD and SUD.

Introduction

The inhibitory neurotransmitter γ-aminobutyric acid (GABA) acts mainly through ionotropic GABA$_A$ and metabotropic GABA$_B$ receptors. GABA$_B$ receptors are coupled to adenylyl cyclase via a G-protein; activation of GABA$_B$ receptors decreases adenylyl cyclase activity, increases potassium conductance, and decreases calcium conductance. As a result, activation of pre – and post-synaptic GABA$_B$ receptors inhibits neuronal

excitability and release of multiple neurotransmitters [1, 2], with several therapeutic potentials [3, 4].

Numerous experimental and clinical studies, conducted over the last 15 years, suggest that pharmacological activation of the $GABA_B$ receptor – by the prototypic $GABA_B$ receptor agonist, baclofen (β-[chlorophenyl]-GABA; Lioresal®; Gablofen®; Kemstro™) or other $GABA_B$ receptor agonists [4, 5] – may suppress a variety of alcohol-, cocaine-, nicotine-, opioid-, and amphetamine-motivated behaviours in rodents, as well as alcohol craving and drinking, consumption of drugs of abuse, and signs and symptoms of withdrawal syndrome from alcohol and opioids in humans.

The present paper is aimed at critically reviewing the lines of preclinical and clinical evidence featuring baclofen as a potentially effective pharmacotherapy for alcohol use disorder (AUD) and substance use disorder (SUD). This paper also reviews recent preclinical data on the anti-addictive properties of the positive allosteric modulators (PAMs) of the $GABA_B$ receptor, a new class of $GABA_B$ receptor ligands with potential therapeutic advantages compared to baclofen.

Baclofen: preclinical evidence of its "anti-addictive" properties

At preclinical level, multiple and – for the most part – consistent lines of experimental evidence indicate that acute or repeated treatment with non-sedative doses of baclofen suppressed several alcohol-related behaviours and alcohol psychopharmacological effects in rats and mice [6, 7]. Specifically, baclofen administration has been reported to suppress: (a) signs of alcohol withdrawal syndrome – including anxiety-related behaviours, tremors, and seizures – in rats made physically dependent on alcohol; (b) acquisition and maintenance of high alcohol drinking under the 2-bottle "alcohol vs. water" choice regimen in rats; (c) the increase in alcohol intake occurring in rats after a period of forced abstinence from alcohol (experimental model of alcohol relapse); (d) binge-like alcohol drinking (a single, brief episode of excessive drinking) in mice; (e) the increase in alcohol drinking induced by treatment with opioid and cannabinoid receptor agonists (possible model of the so-called "gateway hypothesis", i.e. the facilitated transition between two abusive drugs) in rats; (f) alcohol reinforcing properties in rats and mice trained to press a lever to access alcohol under a fixed ratio schedule of responding; (g) alcohol motivational properties in rats, measured as the maximal amount of "work" (in terms of lever-pressing) that rats are willing to perform in seeking alcohol (experimental model of the human craving for alcohol); (h) reinstatement of alcohol-seeking behaviour triggered in rats by an experimenter-delivered complex of cues previously associated to alcohol availability (another experimental model of alcohol relapse); (i) alcohol-induced conditioned place preference (measure of alcohol rewarding properties) in mice; (j) alcohol-induced stimulation of locomotor activity (measure of alcohol stimulatory and euphorigenic-like properties) in rats and mice.

Multiple studies have extended the capacity of baclofen to suppress alcohol-motivated behaviours to several other drugs of abuse [6]. Specifically, treatment with baclofen – administered both systemically and into specific areas of the brain "reward" system – has been reported to reduce: (a) lever-pressing for intravenous self-administration of cocaine, nicotine, amphetamine, methamphetamine, morphine, heroin, and γ-hydroxybutyric acid in rats and mice; (b) reinstatement of cocaine-, nicotine-, and heroin-seeking behaviour in rats; (c) nicotine-, amphetamine-, methamphetamine-, and morphine-induced conditioned place preference in rats and mice; (d) cocaine-, nicotine-, and amphetamine-stimulated hyperlocomotion as well as cocaine-, amphetamine-, and morphine-induced locomotor sensitization in rats and mice; (e) multiple withdrawal signs in rats and mice made physically dependent on nicotine and morphine.

Together, these data suggest that the GABA$_B$ receptor is a major component of the neural substrate mediating the central effects of several drugs of abuse. Most of the above data have been collected using experimental models with predictive validity for the human disease, underlining the relevance of these data in terms of translation to the clinics. The above results have been obtained testing doses of baclofen that were, in many instances, devoid of sedative effects; it should be noted, however, that the anti-addictive effects of baclofen were often produced by doses not far from those producing sedation and motor-incoordination (the animal correlate of the human side effects), suggestive of a narrow therapeutic window.

In terms of mechanism of baclofen action, GABA$_B$ receptors located both pre – and post-synaptically (on glutamatergic and dopaminergic neurons, respectively) in the ventral tegmental area (VTA) (a key area of the brain "reward" system) constitute the likely site of baclofen action: their activation by baclofen indeed exerted an inhibitory action on dopamine neurons projecting from the VTA to the nucleus accumbens, suppressing the increase in dopamine release stimulated by drugs of abuse [6–8]. Accordingly, several of the above-mentioned anti-addictive effects of baclofen have been replicated after baclofen injection directly into the rat or mouse VTA.

Baclofen: clinical evidence of its anti-addictive properties

The pharmacological treatment of AUD and SUD is aimed at (a) helping patients to achieve abstinence or, at least, reduce the consumption of alcohol and other drugs of abuse, (b) reducing the risk of relapse, (c) reducing the severity of craving (defined as the intense desire or strong urge for alcohol or a given drug), (d) decreasing the severity of withdrawal symptoms, and (e) reducing the severity of possible comorbid disorders (e.g., anxiety).

Baclofen was introduced in clinical use for the treatment of muscle rigidity in the early 1960s [9]. Following oral administration, baclofen is rapidly absorbed and up to 80% of the dose is excreted in the urine, with only a limited hepatic metabolism [9]. Side effects are generally mild, most frequently represented by sedation, weak-

ness, and vertigo; these usually disappear with continued therapy. These side effects are dose-related and are manifested at doses higher than 60 mg/day. Notably, patients with impaired renal function are at particular risk of baclofen accumulation, even on low-dose therapy. Kidney, and not liver, elimination is seen as a therapeutic advantage for patients with AUD and SUD, as they frequently develop liver diseases.

Four randomized, controlled trials (RCTs) have investigated the efficacy of baclofen in the treatment of AUD [10–13]. These RCTs recruited a total of 245 patients. Baclofen daily dose ranged from 30 [10–12] to 60 [13] mg, divided in 3 daily administrations. Treatment length ranged from approximately 4 [10] to 12 [11–13] weeks. Two of the RCTs [10, 11] found that baclofen was effective in (a) increasing the number of patients who achieved abstinence, (b) decreasing alcohol consumption in patients who did not achieve abstinence, (c) reducing craving severity, and (d) reducing anxiety scores. Notably, one of the RCTs [11] included patients with liver cirrhosis. The other 2 RCTs [12, 13] failed to demonstrate a significant effect of baclofen treatment. Specifically, one RCT [12] reported no change in (a) rate of heavy drinking days, (b) rate of abstinent days, and (c) alcohol craving; nevertheless, baclofen treatment reduced anxiety scores. The last RCT [13] was initially designed as an international, multi-centre study; unfortunately, it did not achieve the preplanned level of participation. A sub-analysis of the Italian patient cohort found a dose-related reduction of alcohol consumption in baclofen-treated patients. In all these RCTs, side effects were reported to be tolerable, even in patients affected by liver cirrhosis.

Six RCTs investigated baclofen efficacy in the treatment of SUD [14–19]. These RCTs recruited a total of 448 patients (cocaine use disorder: 230 [15, 18]; opioid use disorder: 40 [14]; nicotine use disorder: 60 [17]; nicotine use disorder and AUD: 30 [19]; methamphetamine use disorder: 88 [16]). Baclofen daily dose ranged from 60 [14–16, 18] to 80 [17, 19] mg, divided in 3–4 daily administrations. Treatment length ranged from approximately 6 to 16 weeks. The 2 RCTs focusing on nicotine use disorders (and using a daily dose of baclofen of 80 mg) found that patients benefitted from baclofen treatment. Specifically, baclofen (a) reduced the daily number of cigarettes smoked, although none of the participants quit smoking [17], and (b) increased the number of days of abstinence from alcohol and tobacco co-use [19]. Conversely, the other 4 RCTs [14–16, 18] provided less conclusive results. The RCT focusing on opioid use disorder [14] found that baclofen treatment reduced craving for and use of opioids, without achieving statistical significance. The first RCT on cocaine use disorder [15] identified a positive medication effect for baclofen on cocaine use; the second RCT on cocaine use disorder [18], including a larger sample of patients with a more severe cocaine use disorder, failed to find any baclofen efficacy. Finally, the only conducted RCT on methamphetamine use disorder [16] found a treatment effect in those patients with higher compliance. In all RCTs, baclofen was devoid of serious side effects.

Two RCTs investigated baclofen efficacy in the treatment of withdrawal symptoms from heroin [20] or alcohol [21]. A total of 106 patients (44 and 62 patients with alcohol and opiate withdrawal syndrome, respectively) were recruited. Baclofen daily dose was around 30 mg. Treatment period was 3 [21] to 14 [20] days. Both studies found that baclofen reduced the severity of withdrawal syndrome. Specifically, baclofen reduced the severity of alcohol withdrawal syndrome and benzodiazepine use [21] and was more effective and faster-acting than clonidine in counteracting opiate withdrawal symptoms [20].

The relatively low number of RCTs conducted to date, together with the discrepancy in the results collected, does not allow any definitive conclusions to be drawn as to on baclofen efficacy in the treatment of AUD and, particularly, SUD. However, the majority of these RCTs tested relatively low doses of baclofen (30–60 mg/day) [10–16, 18, 20, 21] and excluded patients with other mental disorders [10, 11, 13–17, 19, 20]. Interestingly enough, and at variance with the design of these RCTs, a series of multiple case reports found that administration of higher doses of baclofen (up to 400 mg/day, divided into 3 daily administrations), completely suppressed alcohol intake in a sample of AUD patients including subjects with other mental disorders. An eloquent example is constituted by the dose-finding trial conducted by Olivier Ameisen, a French physician and alcoholic, who treated his own AUD and anxiety with increasing daily doses of baclofen [22]. Daily doses of baclofen as high as 270 mg completely suppressed his craving for and consumption of alcohol. Due to somnolence, Ameisen progressively reduced baclofen dose to 120 mg/day: with this dose, Ameisen maintained abstinence and craving suppression in the absence of any side effects. Other case reports confirmed that administration of high doses of baclofen was effective and safe in patients with AUD and other psychiatric illnesses [23–25]: patients achieved abstinence from alcohol without manifesting side effects secondary to the combined use of baclofen and psychoactive medications (e.g., antidepressants, anti-psychotics, and anxiolytics).

The efficacy of baclofen in reducing anxiety was observed in several RCTs [10–12] and case reports [22–25], suggesting that this may contribute towards the capacity of baclofen to reduce alcohol craving and consumption. However, it should be noted that the coexistence of a mental disorder may delay response to baclofen [9].

Further studies are needed to better understand the potential efficacy of baclofen in the treatment of AUD and SUD. Over the forthcoming months, the results of RCTs currently underway in France will help to (a) clarify whether high doses of baclofen are a preferable therapeutic option compared to low doses and (b) better understand the relationship between the typology of AUD and SUD patients (e.g., presence of other mental disorders) and baclofen response.

Information currently available does not support baclofen administration as the first-line pharmacological option for AUD and SUD. However, baclofen may represent

a valuable option use in for patients with AUD or SUD who: a) fail to respond to other approved medications, b) are affected by liver disease (preventing the administration of medications metabolized by the liver), and c) are affected by SUD for which no approved medication is available. At present, and awaiting clarification of the therapeutic potential of high baclofen doses, a reasonable treatment schedule would include: a) an initial dose of 15 mg baclofen (divided into 3 daily administrations), b) evaluation of craving severity at this initial baclofen dose, and – if needed – c) progressive increase of baclofen daily dose up to a dose capable of achieving a maintaining suppression of craving and intake. It is important that patients' renal function should be carefully assessed before commencing baclofen therapy. Treatment with baclofen should always be conducted under strict medical supervision; patients should be advised against abrupt baclofen discontinuation.

Positive allosteric modulators (PAM): preclinical evidence of their anti-addictive properties

$GABA_B$ PAMs constitute an important advancement in the pharmacology of the $GABA_B$ receptor. $GABA_B$ PAMs bind to a distinct site from the orthosteric agonist binding site of GABA (and baclofen) and are devoid of substantial intrinsic agonistic activity in the absence of GABA; GABA PAMs act synergistically with GABA, enhancing its effects only in those synapses where GABA has endogenously been released [5]. This mode of action results in potential advantages over baclofen: $GABA_B$ PAMs activate the receptor without the limitations (e.g., receptor overstimulation and desensitization, overdosage, development of tolerance) associated with agonist activation. Data collected to date invariably demonstrate that, compared to baclofen, $GABA_B$ PAMs feature a much larger separation between the "desired" (anxiolysis, anti-addiction) and "undesired" (sedation, motor-incoordination) pharmacological effects [6–8].

Several anti-addictive effects of baclofen are reproduced by treatment with $GABA_B$ PAMs [6–8]. Recent research has indeed demonstrated that administration of the in vivo effective $GABA_B$ PAMs, CGP7930, GS39783, BHF177, rac-BHFF, and ADX71441, reduced: a) acquisition and maintenance of high alcohol drinking in rats; b) binge-like alcohol drinking in rats and mice; c) oral alcohol self-administration in rats; d) intravenous self-administration of cocaine and nicotine in rats; e) reinstatement of cocaine – and nicotine-seeking behaviour in rats; f) nicotine-, amphetamine-, and methamphetamine-induced conditioned place preference in rats; g) cocaine-, nicotine-, and amphetamine-stimulated hyperlocomotion in mice; h) withdrawal signs in rats and mice made physically dependent on nicotine and morphine.

In line with their molecular mode of action, repeated treatment with $GABA_B$ PAMs did not result in development of tolerance to their anti-addictive effects (if ideally transposed to humans, lack of tolerance is seen as a fundamental condition for a pharmacotherapy for AUD or SUD). Additionally, combined treatment with $GABA_B$

PAMs and baclofen potentiated the anti-addictive effects of baclofen, while its sedative effects were virtually unchanged; in terms of translation to the clinic, these data suggest that combination of low doses of both baclofen and GABA$_B$ PAMs would potentiate the "desired" pharmacological effects of baclofen with no change on its "undesired", sedative and muscle-relaxant effects.

Based on these results, GABA$_B$ PAMs may represent a new therapeutic option for use in the treatment of AUD and SUD. The recent transition of ADX71441 to the first steps of clinical trials makes testing its anti-addictive pharmacological profile in humans a feasible and promising option in the near future.

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