Chapter 17
Baclofen: Therapeutic Use and Potential of the Prototypic $GABA_B$ Receptor Agonist

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Abstract Baclofen (β-chlorophenyl GABA) is a stereospecific agonist at GABA type B ($GABA_B$) receptors and is inactive at $GABA_A$ receptors. It has therefore been employed as a marker for $GABA_B$ sites. Its selectivity for this receptor provides a unique pharmacology which is covered in this chapter. Numerous effects have been reported but currently only its anti-spasticity and analgesic actions are utilized in clinical medicine. It is the preferred treatment in spasticity of different origins. Its potential for use in other conditions, for example, in reducing drug addiction, in the treatment of gastroesophageal reflux disease, chronic cough and hiccup is very strong. However, as it is a directly acting receptor agonist its action is likely to be diminished by desensitization. Moreover, its access to the CNS is limited requiring the administration of high doses. This increases the chance of unwanted side effects. To overcome this in spasticity, the administration of lower doses into the intrathecal space through an indwelling cannula has had a major influence on the acceptance of the drug by patients. In other conditions, an alternative approach is required and the possible solution may be the use of positive allosteric modulators of the $GABA_B$ receptor. This could reduce receptor desensitization and improve access to the site of action.

Keywords Baclofen • Spasticity • Analgesia • Epilepsies • Antidepressant • Cognition • Addiction • Hiccup • Cough • Gastroesophageal reflux disease

β-Chlorophenyl GABA (Baclofen) was first introduced into clinical medicine in 1972 after evidence was obtained showing it had a muscle relaxant effect in an animal model (Bein 1972). It was designed to be a GABA-mimetic, which could cross the blood–brain barrier through increased lipophilicity (Keberle and Faigle 1968). Whilst it is able to gain access to the brain after peripheral administration, this is not due to passive diffusion but instead it appears to enter via a neutral amino acid transporter (van Bree et al. 1988, 1991). Although baclofen was designed to mimic the

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action of γ-aminobutyric acid (GABA), there was no evidence, when it was first used clinically, that it acted in this manner. Numerous in vitro studies failed to show any activity at the GABA receptor (Curtis et al. 1974; Davies and Watkins 1974). Only some 10–5 years later did evidence emerge that supported an interaction with a GABA receptor that is not associated with chloride ion channels. It was this selective effect at a metabotropic GABA receptor that provided, in part, the basis for the existence of a novel receptor, which we designated GABA type B '$GABA_B$' receptor (Hill and Bowery 1981).

Activation of this receptor in brain tissue can produce neuronal hyperpolarization or a decrease in evoked neurotransmitter release. The former effect is mediated by K^+ conductance predominantly via postsynaptic receptors (Luscher et al. 1997) whilst the latter effect is due to an action on presynaptic terminals mediated via a decrease in membrane Ca^{2+} conductance (Dunlap 1981; Doze et al. 1995; Isaacson 1998; Wu and Saggau 1995). Both of these mechanisms are coupled to G-proteins that are members of the pertussis toxin-sensitive family $G_{io}/G_{o\alpha}$ (Odagaki and Koyama 2001; Odagaki et al. 2000) although some presynaptically mediated events, associated with reduced Ca^{2+} conductance, appear to be insensitive to pertussis toxin (Harrison et al. 1990).

Multiple types of K^+ channels seem to be associated postsynaptic $GABA_B$ receptors (Wagner and Deakin 1993) whilst the predominant calcium channel linked to $GABA_B$ sites appears to be the 'N' type although 'P' and 'Q' type channels have also been implicated (Santos et al. 1995; Lambert and Wilson 1996; Barral et al. 2000). $GABA_B$ sites are also associated with adenylyl cyclase, which is normally inhibited by receptor activation (Xu and Wojcik 1986) although when the enzyme is activated by a G_s-coupled receptor agonist such as isoprenaline, $GABA_B$ receptor activation increases the formation of cyclic adenosine monophosphate (cAMP) above the level produced by isoprenaline alone (Karbon et al. 1984; Hill 1985).

Throughout these studies baclofen (and GABA) has been used as the $GABA_B$ receptor agonist.

17.1 Actions of Baclofen

The actions of baclofen in mammals are not confined to the brain which is hardly surprising given that $GABA_B$ receptors have been shown to be present in many peripheral tissues (Giotti et al. 1990; Erdo and Bowery 1986). The receptors are not even confined to nervous tissue (Erdo and Bowery 1986), but the majority of receptor activation stems from an action on neural systems. $GABA_B$ receptors are widely distributed throughout the mammalian brain although there are regional variations. Whilst there are high receptor densities in the interpeduncular nucleus, dorsal horn of the spinal cord, the thalamic nuclei, cerebellar molecular layer and cerebral cortex, the densities in other brain regions are much lower (Bowery et al. 1987; Chu et al. 1990). Unfortunately, the receptor density does not necessarily reflect the physiological importance of the receptor in all brain regions. For example, in the hippocampus the

Table 17.1 Site of action and potential therapeutic application of baclofen and $GABA_B$ receptor activation

Effect	Site of action	Clinical
Muscle relaxation	Spinal cord reflexes	Spasticity
Antinociception	Spinal cord sensory fibres	Analgesia
	Thalamus	
Antitussive	Cough centre in medulla	Cough suppression
Suppression of drug addiction	Mesolimbic system	Drug abuse
Oesophageal sphincter relaxation	Intestine	Gastroesophageal reflux disease
Smooth muscle relaxation	Lung	Asthma
Food intake modified	Higher centres	Enhance feeding
Insulin/glucagon release	Pancreas	Diabetes
Adenylyl cyclase inhibition	Pancreas	Adenocarcinoma
Reduction in fat intake	Higher centres	Binge eating
Enhancement of neutrophil chemotaxis	Leucocytes	Inflammation
Suppression of pain behaviour	Dorsal periaqueductal grey	Anxiety/panic disorder

overall receptor density, as assessed by receptor autoradiography, appears to relatively low although there is variation within the structure. Many studies have been conducted using hippocampal tissue, and this structure provided the initial evidence for a physiological role of the $GABA_B$ receptor (Dutar and Nicoll 1988; Nicoll 2004).

Table 17.1 summarizes the effects of baclofen throughout the mammalian system with the sites of action implicated in each case. We can consider each locus in turn examining what effect(s) has been observed and how this may relate to any clinical potential.

17.2 Spasticity

Numerous studies have been performed on the action of baclofen in the spinal cord. In initial studies using GABA in vivo in anaesthetized animals, it was shown that it depresses all types of spinal neurons and could inhibit monosynaptic and polysynaptic reflex activity (Curtis and Watkins 1965). In a preliminary report using baclofen as a GABA derivative, Birkmayer et al. (1967) were able to show control of spasticity after spinal cord lesions. Subsequent clinical studies supported this finding in a placebo-controlled trial in 6 patients (Jones et al. 1970) and in a double-blind trial in 23 patients (Hudgson and Weightman 1971). Baclofen rapidly became the drug of choice in spasticity in patients with hemi- and tetraplegia (Brogden et al. 1974), in multiple sclerosis (Giesser 1985; Brar et al. 1991; Smith et al. 1991) in cerebral palsy (Buonaguro et al. 2005; Scheinberg et al. 2006; Krach 2009; Navarrete-Opazo et al. 2016) in stiff-man syndrome (Whelan 1980; Silbert et al. 1995; Stayer et al. 1997) tetanus (Mueller et al.

Table 17.2 Possible unwanted side effects of baclofen after oral administration

Nausea
Drowsiness
Dizziness
Hypotension
Seizures
Muscle weakness
Hallucinations
Mental disturbance

1987; Demaziere et al. 1991; Engrand et al. 1999; Santos et al. 2004) and after stroke (O'Brien et al. 1996). The underlying effect of baclofen in these conditions is a reduction in spinal reflex mechanisms, but how this arose was not established. No evidence for an action at GABA receptors was obtained. Although baclofen had a beneficial effect in spasticity, it has many unwanted side effects (Table 17.2) primarily because it had to be administered orally in large doses due to poor penetration into the brain. In 1984, Penn and Kroin (1984, 1985) made an important discovery that baclofen could be administered intrathecally using an indwelling mini-pump. This enabled much smaller doses to be given as Leisen et al. (2003) demonstrated; an intrathecal dose of 600 μg baclofen produced a local plasma level of 5–20 ng/g whereas 100 mg baclofen given orally produced a level of <3 ng/g in cerebrospinal fluid (CSF). Numerous studies have been made since the Penn and Kroin (1984) original report and in all cases positive effects have emerged following intrathecal application (Ochs 1993; Becker et al. 1997; Gianino et al. 1998; Rawlins 1998; Sasaki and Ogiwara 2016; Heetla et al. 2016; Bonouvrie et al. 2016; Okazaki et al. 2016; Al-Kadalry et al. 2015; Naito 2014; Khurana and Gang 2014; Mathur et al. 2014).

17.3 Analgesia

Baclofen has been shown to be anti-nociceptive in animal models of acute pain. For example, in the rat tail flick and hot plate tests at doses lower than required to produce muscle relaxation (Wilson and Yaksh 1978; Aley and Kulkarni 1991). Visceral pain-related responses to colorectal distension in rats are also inhibited by baclofen (Brusberg et al. 2009). An analgesic effect of baclofen in clinical medicine has been noted in cluster headache, migraine and trigeminal neuralgia (Hering-Hanit and Gadoth 2000; Hering-Hanit 1999; Fromm et al. 1980, 1984; Fromm and Terrence 1987). However, following its systemic administration rapid tolerance to the effects of baclofen occurs, and this limits its use as an analgesic.

The sites of action of baclofen responsible for analgesia are within the spinal cord and thalamus. Systemic, intrathecal or injection into discrete regions of the thalamus can produce analgesia in acute pain models (Cutting and Jordan 1975; Sawynok and LaBella 1982; Vaught et al. 1985). Whilst spinal transection reduces the anti-nociceptive effect

of baclofen (Proudfit and Levy 1978), there is evidence for a distinct contribution from a reduction in primary afferent transmitter release within the spinal cord. $GABA_B$ receptor activation in spinal cord slices prevents the release of Substance P, glutamate and calcitonin gene-related peptide (CGRP) evoked by electrical stimulation of the dorsal roots (Malcangio and Bowery 1993, 1996; Teoh et al. 1996). All three compounds are believed to contribute to the transmission of nociceptive impulses in the spinal cord. If a $GABA_B$ receptor antagonist is administered to the isolated spinal cord preparation, there is no increase in transmitter release. However, if chronic inflammation is produced by in vivo administration of Freunds adjuvant this produces an increase of around 25% in the concentration of GABA in the dorsal horn (Castro-Lopes et al. 1992). This facilitates the $GABA_B$ receptor control of Substance P release. When a $GABA_B$ receptor antagonist is applied to the isolated cord prepared from adjuvant-treated rat, the evoked release of Substance P is dramatically increased (Malcangio and Bowery 1994). Furthermore, if the GABA antagonist is administered to the intact adjuvant-treated rat, there is a striking increase in nociception. This contrasts with the lack of effect of the antagonist in naïve animals. This would suggest that during chronic inflammation there is an increase in $GABA_B$ innervation to primary afferent terminals that acts as a pathological anti-nociceptive control to oppose the enhanced sensory input that occurs.

Administration of baclofen into the thalamic ventrobasal complex contralateral to the inflamed joint in monoarthritic rats can attenuate allodynia in the ankle-bend test (Potes et al. 2006) supporting a higher centre role in nociception. However, evidence for a spinal role is also strong. $GABA_B$ receptor expression is required for inhibition of N-type (Cav 2.2) calcium channels by α-conotoxins in rat models of neuropathic pain. Conotoxins are anti-nociceptive. Knockdown of $GABA_B$ receptors in rat-isolated dorsal root ganglia using RNA interference produced a significant reduction in the inhibition of N-type calcium channels produced by baclofen. This would indicate that $GABA_B$ receptor activation must occur to allow the modulation of N-type calcium channels and consequent analgesia by α-conotoxins (Cuny et al. 2012; Huynh et al. 2015)

Further support for the involvement of $GABA_B$ receptors in pain mechanisms comes from studies with 'knock-out' mice (Schuler et al. 2001) in which the subunits $GABA_{B1}$ or $GABA_{B2}$ are not formed. In either case, functional $GABA_B$ receptors are not produced and hyperalgesia occurs indicating that heteromeric receptors are required to maintain nociceptive thresholds.

As indicated earlier, the potential for baclofen as a clinical analgesic is limited by rapid tolerance and the adverse effects which can develop after systemic administration (Table 17.2). The introduction of positive allosteric modulators of the $GABA_B$ receptor has provided an alternative approach to reduce both tolerance and unwanted side effects.

Many examples of $GABA_B$ positive allosteric modulators have been described (see Chap. 18 of this volume) and tested in vivo in a variety of animal models for anti-nociceptive activity. For example, ADX 71943 reduced the pain-associated behaviours in the acetic acid writhing and formalin tests in mice and the $GABA_B$ antagonist, CGP63360, blocked this effect. The compound was inactive in the marble burying and elevated plus maze tests for anxiolytic or anxiogenic activity (Kalinichev et al. 2014). Baclofen produces anti-nociceptive effects in animal models of visceral pain including mechanically

Table 17.3 Comparison of effects of baclofen and positive allosteric modulators of $GABA_B$ receptors

Effect	Baclofen	Positive allosteric modulator
Tolerance	Yes[a]	No[b]
Anti-nociception	Yes[c]	Yes[d]
Body temperature	Decrease[e]	No effect[f]
Gastroesophageal disease	Reduction[g]	?
Systemic blood pressure	Decrease (in hypertension)[h]	?
Sedation	Yes[i]	No[f]
Myorelaxation (locomotor activity↓)	Yes[j]	No[f]
Cognition	Decrease[k]	?
Food intake	Increase[l]	Increase[l]
	Decrease[m]	Decrease[m]
Anticonvulsant	Yes[n]	Yes[o]
Overactive bladder	Reduces[p]	Reduces[q]
Anxiety	Anxiogenic/variable[r]	Anxiolytic[f]
Drug addiction (nicotine, cocaine, opiates, alcohol)	Decrease[s]	Decrease[b]

Table 17.3 References (numbers after each effect refer to reference list below):
[a]Gjoni T, Urwyler S (2008) Neuropharmacology 55: 1293–1299
[b]Ong J, Kerr DI (2005) CNS Drug Rev 11: 317–334
[c]Brusberg M, Raynefjord A, Martinsson R et al. (2009) Neuropharmacology 56: 362–367
[d]Kalinichev M, Donovan-Rodriguez T, Girard F et al. (2014) Br J Pharmacol 171: 4941–4954
[e]Queva C, Bremner-Danielsen M, Edlund A et al. (2003) Br J Pharmacol 140: 315–322
[f]Cryan JF, Kelly PH, Chaperon F et al. (2004) J Pharmacol Exp Ther 310: 952–963
[g]Miner PB jr, Silberg DG, Ruth M et al. (2014) Gastroentorology 14: 188
[h]Li DP, Pan HL (2010) Adv Pharmacol 58: 257–286
[i]From A, Heltberg A (1975) Acta Neurol Scand 51: 158–166
[j]Stefanski RI, Plaznik A, Palejko W, Kostowski WJ (1990) J Neural Transm Park Dis Dement Sect 2(3): 179–191
[k]Stackman RJ, Walsh TJ (1994) Behav Neural Biol 61: 181–185
[l]Ebenezer IS (2014) Eur J Pharmacol 690: 115–118
[m]Perdona E, Costantini VJ, Tessari M et al. (2011) Neuropharmacology 61: 957–966
[n]Brown JW, Moeller A, Schmidt M et al. (2016) Neuropharmacology 101: 358–367
[o]Mares P, Ticha K, Mikulecki A (2013) Epilepsy Behav 28: 113–120
[p]Frost F, Nanninga J, Penn R et al. (1989). Am J Phys Med Rehabil 68: 112–115
[q]Kalinichev M, Palea S, Haddouk H, et al. (2014) Br J Pharmacol 171: 995–1006
[r]Cryan JF, Slattery DA (2010) Adv Pharmacol 58: 427–451
[s]Viachou S, Markov A (2010) Adv Pharmacol 58: 315–371

induced visceral pain. CGP7930, a positive allosteric modulator (Adams and Lawrence 2007), is also anti-nociceptive in such a model (Brusberg et al. 2009) and rac-BHFF, another positive allosteric modulator, enhances baclofen-mediated anti-nociception in neuropathic mice (Zemoura et al. 2016). This would suggest that positive allosteric modulators may provide a better approach to analgesia having less unwanted side effects. Positive allosteric modulators appear to have an improved profile compared to baclofen or other direct acting agonists (Table 17.3).

17.4 Epilepsy: Convulsant Seizures

GABA receptors have long been associated with the control of epileptic seizures. Deficits in GABA type A ($GABA_A$) receptor function within the central nervous system (CNS) provide an underlying mechanism for the production of seizures (Gale 1992; Olsen et al. 1992) and positive allosteric modulation of $GABA_A$ receptors with benzodiazepines can reduce seizure activity (Upton and Blackburn 1997). However, $GABA_B$ receptors have also been implicated (Gamardella et al. 2003; Pacey et al. 2009, 2011; Vienne et al. 2010). 'Knock-out' mice lacking functional $GABA_B$ receptors exhibit both spontaneous and audiogenic-induced seizures (Prosser et al. 2001; Schuler et al. 2001; Vienne et al. 2010), and baclofen is known to produce anticonvulsant effects in the DBA/2J mouse audiogenic seizure test (Meldrum and Horton 1980; Brown et al. 2016). However, baclofen appears to augment some seizures whilst inhibiting others. For example, it has been shown to increase the incidence of seizures evoked by pentylenetetrazole without increasing seizures due to local injections of excitatory amino acids (Snodgrass 1992).

In temporal lobe epilepsy, impairment of $GABA_B$ receptor function has been noted in cerebrocortical slices obtained from patients undergoing surgery for drug-resistant epilepsy (Teichgraber et al. 2009) suggesting that $GABA_B$ receptor activation could be important in seizure suppression.

17.5 Epilepsy: Absence Seizures

The characteristic electroencephalography (EEG) activity of a 3-Hz spike and wave, which is manifest during typical absence seizures, appears to stem from discharges in the thalamic nuclei. But this is probably not the site of origin of these discharges. Meeren et al. (2005) have demonstrated unequivocally in a genetic rat model of absence epilepsy (Wistar Albino Glaxo/Rij-rat, WAG/Rij) that the origin is outside the thalamus in the perioral region of the somatosensory cortex. These discharges spread across the cortex and initiate a corticothalamic cascade.

Inaba et al.(2009) examined the effects induced by baclofen (0.1–10 μM) on the inhibitory events recorded in vitro from neocortical slices obtained from these epileptic WAG/Rij (>180 day-old) and from age-matched, non-epileptic control (NEC) rats. They found that higher doses of baclofen were required to depress pharmacologically isolated, stimulus-induced inhibitory postsynaptic potentials (IPSPs) generated in WAG/Rij neurons as compared to those in NEC neurones. These authors suggest that this indicates a decreased function of presynaptic $GABA_B$ receptors in the WAG/Rij rat neocortex.

In another rat model of absence seizures (genetic absence epilepsy rat of Strasbourg, GAERS), when baclofen is injected into the ventrobasal thalamus or reticular nucleus this exacerbates the seizures (Manning et al. 2003). Conversely, if a $GABA_B$ antagonist is injected into the same brain regions this suppresses the seizures. These studies in a rat

model may implicate the $GABA_B$ receptor in the generation or modulation of absence seizures but certainly indicates that baclofen might exacerbate seizures clinically and, therefore, would be contraindicated in patients with absence epilepsy.

Another model, this time in mice, DBA/2J, which are prone to audiogenic seizures (see above) also provides an in vivo system for studying spontaneous absence seizures. Baclofen, administered i.p. (0.5–10 mg/kg), dose-dependently increased the number of spike and wave discharge episodes in this model. This increase was also reversed by the $GABA_B$ antagonist, SCH50911 (50 mg/kg i.p.) (Bortolato et al. 2010).

Atypical absence epilepsy is another distinct form of absence in which the seizures differ markedly from those in typical absence seizures notably in the EEG pattern. A model of this disorder can be produced in rats treated with the cholesterol synthesis inhibitor, AY-9944 (Cortez et al. 2001). In this animal model, the spike and wave discharges are significantly prolonged by baclofen and abolished by the $GABA_B$ antagonist, CGP 35348 (Cortez et al. 2001). Over expression of the $GABA_B$ receptor 1a subtype in transgenic mice also appears to produce atypical absence seizures which are exacerbated by baclofen (Wu et al. 2007).

Taken together these data support a role for $GABA_B$ receptors in the aetiology of both typical and atypical absence epilepsy.

17.6 Affective Disorders

Lloyd et al. (1985) and Lloyd (1989) were the first to report that a variety of antidepressant drugs, e.g. fluoxetine, citalopram and amitriptyline given chronically (6–18 days) in rats, produces a significant upregulation in $GABA_B$ binding sites in the frontal cortex. By contrast neuroleptics, psychostimulants and anxiolytics had no effect (Lloyd 1989). From the data produced by Lloyd (1989) there would appear to be a close connection between $GABA_B$ receptor mechanisms and cerebral beta-adrenoceptors. Repeated administration of baclofen to rats produces a down-regulation in cerebral adrenoceptors in a manner similar to chronic treatment with nomifensine or imipramine (Suzdak and Gianutsos 1986). Although these observations were disputed (Cross and Horton 1987, 1988), there is now good evidence that $GABA_B$ mechanisms are associated with depression. Baclofen administered to rats undergoing the forced swim test and the learned helplessness test, which are animal models for determining the action of antidepressant drugs, attenuates the action of recognized antidepressant drugs such as mianserin and desipramine (Nagakawa et al. 1996; see Chap. 12 of this volume). However, baclofen given alone had no direct effect in these models whereas $GABA_B$ receptor antagonists administered to mice in the forced swim test produced an antidepressant-like effect (Mombereau et al. 2004). Knock-out mice lacking $GABA_{B1}$ or $GABA_{B2}$ receptor subunits exhibit antidepressant behaviour and anxiety (Mombereau et al. 2004). So we might conclude that a reduction in $GABA_B$

receptor function produces antidepressant-like behaviour whilst an increase in receptor activation produces a depressant effect. But baclofen does not fit into this category; it merely appears to attenuate the effects of antidepressant drugs.

Very little is known about the potential clinical significance of these observations, as there is a paucity of clinical data. However, Post et al. (1991) found in 3 out of 5 patients with depression that baclofen exacerbated their symptoms.

In a study by Keegan et al. (1983), a patient with pre-existing bipolar affective disorder developed increased depression whilst on baclofen. This led the authors to conclude that baclofen should be used with caution in patients with neuropsychiatric problems.

17.7 Cognitive Behaviour

Baclofen and other $GABA_B$ receptor agonists suppress cognitive behaviour in animals (Carletti et al. 1993; Stackman and Walsh 1994; De Sousa et al. 1994; Pitsikas et al. 2003), and this effect is reversed by $GABA_B$ receptor antagonism (Pitsikas et al. 2003; Liu et al. 2014). Baclofen has also been shown to contribute to different varieties of amnesia in the human brain (Zerman et al. 2016). By contrast, impairment of recognition memory induced in mice by methamphetamine (1 mg/day for 7 days) was ameliorated by baclofen but not by the $GABA_A$ receptor agonist, gaboxadol (Arai et al. 2009). Similarly, in a study performed in Macaca mulatta primates in which cocaine (0.2–0.6 mg/kg iv) induced a cognitive decline in a delayed match to sample task, baclofen, co-administered with cocaine, reversed the task performance back to nondrug (saline iv) control levels (Porrino et al. 2013). Baclofen has also been shown to ameliorate spatial memory impairment induced by chronic cerebral hypoperfusion in rats (Luo et al. 2016). These effects of baclofen seem contrary to previous reports but still implicate $GABA_B$ mechanisms in cognitive function.

Improvement in cognitive behaviour by $GABA_B$ receptor antagonists is well established in a variety of animal models such as in an active and passive avoidance tests in rats and mice (Getova and Bowery 1998; Getova and Dimitrova 2007) and age-related learning in Fischer rats (Lasarge et al. 2009). Intrahippocampal administration of the $GABA_B$ antagonist, 2-hydroxy saclofen (20 μM) markedly reversed the scopolamine-induced impairment in behavioural long-term potentiation (LTP) and maze performance in rats indicating that blockade of the $GABA_B$ receptor displays a facilitatory role in the induction of behavioural LTP and a maze learning task (Liu et al. 2014).

Pentylenetetrazole-kindling-provoked amnesia in rats is also prevented by $GABA_B$ antagonists such as CGP36742 (Genkova-Papazova et al. 2000)

The potential for $GABA_B$ receptor antagonists as cognition enhancers is covered in Chap. 19 of this volume, but there is already evidence of limited clinical effects with the antagonist SGS742 [also known as CGP36742] (Froestl et al. 2004).

17.8 Drug Addiction

A major goal in clinical therapeutics is the successful treatment of drug dependence, and many targets are under consideration. This topic is covered in Chaps. 14 and 15 of this volume, but it seems appropriate to consider baclofen here as it was the first $GABA_B$-related compound to be shown to reduce the reinforcing effects of cocaine in rats (Roberts and Andrews 1997). However, it soon became clear that the addictive behaviour in animals associated with morphine-like substances, nicotine and alcohol could also be attenuated by baclofen and other $GABA_B$ agonists (Xi and Stein 1999; Corrigall et al. 2000; Addolorato et al. 2000, 2002; Cousins et al. 2002; Lorrai et al. 2016). Clinical evidence has been obtained for baclofen reducing alcohol craving in alcoholics (Imbert et al. 2015; Rolland et al. 2015; Chaignot et al. 2015; Lesouef et al. 2014) and reducing the craving for nicotine evidenced by a reduction in the number of cigarettes smoked per day (Colombo et al. 2004; Franklin et al. 2009). Whilst the attenuation of craving for cocaine by baclofen in animals is well established (e.g. Ling et al. 1998; Shoptaw et al. 2003; Haney et al. 2006), the effects in the clinic are not so clear. In a multi-site double-blind study, treatment of severe cocaine-dependent patients with a single dose of baclofen (60 mg/day) for 8 weeks did not show any significant difference from addicts treated with placebo. It was suggested that a higher dose should be tested (Kahn et al. 2009).

One possible area for clinical efficacy is in the use of baclofen for opiate withdrawal (Akhondzadeh et al. 2000), but overall more evidence is required to substantiate the clinical use of baclofen in drug addiction, in part, because of the unwanted side effects of the compound. The advent of positive allosteric modulators of $GABA_B$ sites may provide the answer as preliminary reports seem to suggest (Agabio and Colombo 2014, 2015; Maccioni et al. 2015) and see Chaps. 14, 15, and 18 of this volume.

17.9 Gastroesophageal Reflux Disease

Gastroesophageal reflux disease (GERD) is a disease that affects about 1 in 5 of the population in the western world (Dent et al. 2005) and manifests as heartburn and regurgitation in patients but can give rise to oesophagitis (Wiklund 2004; Vakil et al. 2006). Baclofen can relieve these symptoms, and this was first noted as an unexpected observation in patients treated for spasticity (e.g. Cange et al. (2002). Whilst antacid treatment can help in many cases, persistent symptoms often occur. The $GABA_B$ receptor in the intestine appears to provide a target for inhibiting GERD. Baclofen and other $GABA_B$ receptor agonists inhibit transient lower oesophageal sphincter relaxation, which occurs after a meal and this inhibition appears to be the basis for its beneficial action (Lehmann et al. 1999; see also Chap. 16 of this book)). However, the side effects of baclofen, which result from its access to the brain, would indicate the need for an agent with restricted access. Lehmann

et al. (2009) have described the agonist lesogaberan that has good selectivity for the $GABA_B$ receptor over the $GABA_A$ site and higher affinity than baclofen for $GABA_B$ receptors. This has led to its introduction into clinical trials for GERD (Boeckxstaens et al. 2009) but Astrazeneca have since discontinued these trials although Miner et al. reported a successful randomized placebo-controlled study in 2014.

17.10 Other Actions of Baclofen

Many effects produced by baclofen have been reported since its clinical introduction in 1972. A number of these may be of importance when unwanted side effects are avoided, for example, if and when positive allosteric modulators are pursued clinically.

Baclofen is an antitussive agent and has been shown to be effective in the treatment of chronic refractory cough after systemic administration (Dicpinigaitis and Dobkin 1997; Dicpinigaitis and Rauf 1998; Xu et al. 2013; Chung 2015; see also Chap. 16 of this book). Another interesting action is the suppression of chronic hiccup. In patients with hiccup, over a prolonged period of years baclofen has been shown to stop the hiccup in at least 50 % of them. The mechanism underlying this effect is unclear but may stem from rectifying gastroesophageal abnormalities (Guelaud et al. 1995; Twycross 2003; Turkyilmaz and Eroglu 2008; Steger et al. 2015; Sharma 2015; Zhang et al. 2014; Thompson et al. 2014; Baumann et al. 2014).

Inhibition of vagally and histamine-induced bronchoconstriction by baclofen was first shown by Chapman and colleagues who reported that $GABA_B$ receptor activation in guinea pigs could oppose the bronchoconstriction (for review, see Chapman et al. 1993) Initial suggestions were that baclofen or an analogue might be useful in the clinical treatment of asthma. Although the action of baclofen against histamine was pursued clinically in patients with cervical spinal cord injury, nothing more has emerged with reference to asthma (Grimm et al. 1997). The underlying mechanism for this effect may well be the suppression of Substance P release from nerve terminal in the bronchi.

A major problem in patients with spinal cord lesions is unstable bladder function. Baclofen produces a marked improvement in such cases, which is a beneficial side effect of treatment for spasticity (Taylor and Bates 1979; Nanninga et al. 1989).

17.11 Conclusions

After more than 40 years since its introduction to clinical medicine, baclofen remains the drug of choice in the treatment of spastic disorders. It is by no means the perfect drug producing many unwanted side effects, and therefore improvements are needed. The introduction of positive allosteric modulators of the $GABA_B$ receptor may provide the answer, but their clinical use has yet to emerge. But baclofen has been an extremely

useful compound providing a tool to define the $GABA_B$ site. It was introduced as a muscle relaxant in man before its mechanism of action had been obtained. Only subsequently was its site of action defined (see Chap. 1 of this volume) and since then a multitude of effects, wanted and unwanted, have been reported. The synthesis of analogues has produced more selective agonists such as lesogaberan (Lehmann et al. 2009), which does not cross the blood–brain barrier so well and thus limits its actions to the periphery. However, one important introduction for the application of baclofen to the brain was its administration via the intrathecal route. This meant that much less drug is required which had an enormous influence on the incidence of unwanted side effects. One wonders from where the next improvement will stem.

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