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British Journal of Anaesthesia, 123 (2): e176–e179 (2019)
doi: 10.1016/j.bja.2019.01.030
Advance Access Publication Date: 4 March 2019

Spinal $GABA_A$ receptors for pain control: back to the future?

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γ-Aminobutyric acid type A ($GABA_A$) receptors, ligand-gated ion channel receptors for the inhibitory neurotransmitter GABA, mediate neuronal inhibition in the CNS, including the spinal cord. Based on their subunit compositions (more specifically the α subunit isoform included in the pentameric receptor complex), they can be subdivided into six major subtypes (from α1 to α6). $GABA_A$ receptors containing α1, α2, α3, or α5 subunits are sensitive to modulation by classical benzodiazepines, whereas those containing α4 or α6 subunits instead of α1, α2, α3, or α5 subunits are insensitive. The compound PF-06372865, the subject of a study by Nickolls and colleagues[1] in a recent issue of the *British Journal of Anaesthesia*, was developed by Pfizer Inc (Cambridge, UK) as a partial

DOI of original article: 10.1016/j.bja.2018.12.006.

agonist at the benzodiazepine binding sites of receptors containing α2, α3, or α5 subunits.[1] It is mainly this lack of activity at α1 $GABA_A$ receptors that distinguishes PF-06372865 from classical benzodiazepines. Why is this important, and why should avoiding activity at α1 $GABA_A$ receptors convey analgesic efficacy to benzodiazepine site ligands?

Let us first consider the neurophysiological basis of GABAergic analgesia. This concept is rooted in the gate control theory of pain, in which Melzack and Wall[2] proposed that inhibitory (mainly GABAergic) neurones of the spinal dorsal horn gate incoming nociceptive input and prevent the activation of 'pain' signalling projections by non-painful sensory input. A large body of evidence indicates that the efficacy of this inhibitory control is compromised in chronic pain states through several mechanisms.[3] Accordingly, drugs that facilitate GABAergic inhibition should in principle be able to correct this deficit. Indeed, local spinal administration of drugs that enhance synaptic inhibition reverse heightened pathological pain sensitivity.[4,5] Work in mice expressing genetically engineered $GABA_A$ receptor α subunits has shown that α2 (and α3) $GABA_A$ receptors are the most relevant $GABA_A$ receptor subtypes for spinal analgesia, and that α1 and α5 receptors contribute either nothing (α1) or very little (α5) to this process.[5,6] This profile fits well with the enriched expression of α2 and α3 $GABA_A$ receptors within the spinal dorsal horn, particularly the superficial layers where incoming nociceptive fibres terminate.[7] The dispensability of α1 $GABA_A$ receptors for analgesia was a crucial finding, as receptors of this subtype cause the great majority of the unwanted effects of classical benzodiazepine agonists including sedation, memory impairment, tolerance (loss of efficacy during chronic treatment), and addiction[8] (Fig. 1). This segregation provides a hint as to why sparing activity at α1 receptors would confer analgesic activity.

The clinically tolerated doses of benzodiazepines (for indications other than anaesthesia) are limited by undesired sedation. In fact, typical clinically used doses of classical benzodiazepines yield receptor occupancies <30%.[9–12] Preclinical work has shown that this is too low to yield significant relevant analgesia, explaining why classical non-selective benzodiazepines are basically devoid of analgesic efficacy. Only when activity at α1 $GABA_A$ receptors is sufficiently reduced can the higher doses needed for analgesic efficacy be reached without putting a patient (or an animal) to sleep (see the work of Zeilhofer and colleagues[13]). Inspired by these results, several groups have tested subtype-selective benzodiazepine site agonists in various rodent pain models. Originally, these compounds were developed by groups working in pharma companies, and in academia in the quest for non-sedative anxiolytics. The major outcome of these studies was that such compounds reverse pathological hyperalgesia in most neuropathic and inflammatory pain models and also in postoperative pain, provided that the compounds possessed sufficiently high modulatory activity and were used at sufficiently high doses. Such antihyperalgesic activity does not occur with classical (non-selective) benzodiazepines given systemically. In light of these encouraging preclinical data, scientists have eagerly awaited clinical studies.

The first clinical study of potential analgesic actions of a subtype-selective benzodiazepine site ligand (PF-06372865, the same compound studied by Nickolls and colleagues[1]) did not assess efficacy in experimental human pain, as expected, but rather was a phase II clinical trial in patients with chronic low back pain.[14] This trial yielded clearly negative results. We speculated[15] about the possible reason(s) for this failure such as species differences in target receptor expression and function between rodents and humans, the low predictive value of preclinical read-outs (both very fashionable critiques nowadays), an inappropriate patient population (patients with a neuropathic pain component were actually excluded), and insufficient drug dosing.

The new study provides new insights and helps to further narrow the reasons of the failed low back pain trial. PF-

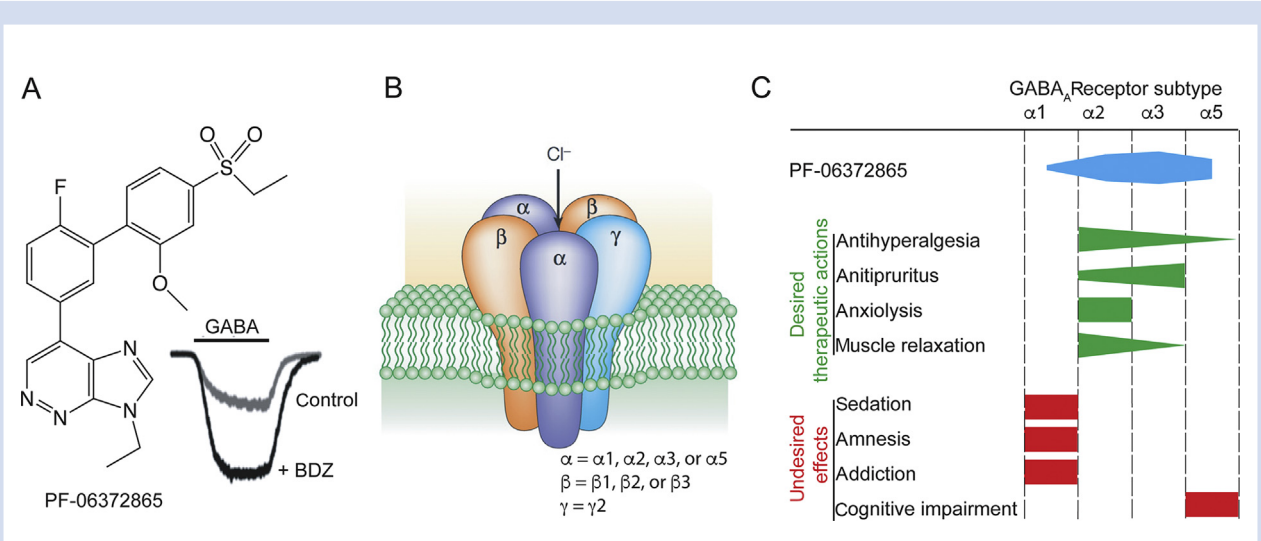

Fig 1. (a) Chemical structure of PF-06372865, a subtype-selective partial agonist at the benzodiazepine-binding site of α2, α3, and α5 γ-aminobutyric acid A ($GABA_A$) receptors. The inset illustrates chloride currents through $GABA_A$ receptor channels recorded in the absence (control) and presence of a benzodiazepine (BDZ). (b) Schematic illustration and subunit composition of heteropentameric $GABA_A$ receptors. (c) Comparison of the subtype-selectivity of PF-06372865 (blue) with the contribution of the different $GABA_A$ receptor subtypes to desired (green) and undesired (red) *in vivo* actions of benzodiazepines.

06372865 was tested in a battery of experimental pain models in healthy volunteers, and its efficacy was compared with that of pregabalin, the current gold standard in neuropathic pain treatment. PF-06372865 proved efficacious in several models with effect sizes comparable with those of pregabalin. Notably, these positive results suggest that selective α2 and α3 $GABA_A$ receptor modulators exert analgesia not only in rodents but also in man, thereby largely ruling out species differences or low predictive values of read-outs in rodent experiments as underlying causes of the failure in the low back pain trial. Instead, the new study supports that insufficient drug dosing was the main problem in the low back pain trial. Nickolls and colleagues[1] tested single doses of 15 and 65 mg that led to estimated receptor occupancy of 50% and 80%, respectively, whereas the low back pain trial used smaller doses of 2.5 and 7.5 mg given twice per day, with estimated peak steady-state α2 $GABA_A$ receptor occupancies of 30% and 50%.[14] Preclinical studies in mice indicated that ~70% of α2 $GABA_A$ receptors need to be drug-bound (even when a high intrinsic activity ligand is used) to achieve a significant reduction in pain thresholds.[6] Therefore, the new study supports a lack of sufficient drug dosing as the most probable reason for failure of PF-06372865 in the low back pain trial. This is further supported by another recently published clinical trial on PF-06372865 that used the same dose regimens as the low back pain trial and failed to demonstrate efficacy against generalised anxiety disorders.[16]

Although the results of Nickolls and colleagues[1] generally support previous preclinical findings in mouse pain models, there are also interesting discrepancies. The most obvious in our opinion is that PF-06372865 showed efficacy against acute nociceptive pain, specifically in the mechanical pressure pain, cold pressor pain, and electrically evoked pain tests in humans. No significant efficacy was detected in acute models of hyperalgesia (the sunburn model) and against heat-evoked pain. PF-06372865 was therefore mostly effective against pain modalities that appeared resistant to $GABA_A$ receptor modulation in mouse experiments.[17] The reasons for these differences are not entirely clear. However, it is tempting to speculate that differences in the read-out measures are relevant. In the human study, PF-06372865 mainly affected pain *tolerance* thresholds but less so pain *detection* thresholds, which were the main readouts in the mouse pain models. Taking these differences into account, the study results are consistent with what could have been predicted from previous preclinical experiments.

Although the new study is far from providing a definitive answer to the ongoing question of translatability in drug research and development, this was never its intended purpose. Importantly, it puts the previous negative result of the low back pain trial into perspective. If insufficient drug dosing was the reason for the failure of the low back pain trial, the good news is that clinical studies published so far have reported excellent tolerability[1,14,16] and suggest that there is significant space for dose augmentation before unwanted effects become dose limiting.

In the film *Back to the Future*, the main character Marty McFly successfully returns home from accidentally being sent 30 yr into the past to find his family in much better circumstances than before he left. This concept, rooted in science fiction, holds some allure in the real-life world of drug research and development. If only we could go back in time and tweak our experimental designs. The film ends with their car converted into a hovercraft flying at the camera and the words 'To be continued…' flashing on the screen. We hope that this is also the case for drugs targeting specific $GABA_A$ receptor subtypes in chronic pain.

Authors' contributions

All authors have contributed equally and approve this editorial.

Declarations of interest

The authors declare that they have no conflicts of interest.

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British Journal of Anaesthesia, 123 (2): e179–e182 (2019)
doi: 10.1016/j.bja.2019.04.042
Advance Access Publication Date: 21 May 2019

Ethical treatment of people with chronic pain: an application of Kaldjian's framework for shared decision-making

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Statement of the problem

Chronic pain is an enormous public health issue with up to 30% of adults in Western countries having chronic pain.[1] Unfortunately, 79% of patients with chronic pain are dissatisfied with their pain care.[2] Healthcare communities may struggle with providing ethical treatment in the context of the opioid crisis first observed in the USA and now seen across Europe, Canada, and Australia.[3] In contrast, inequalities in the global under-treatment of pain have been documented across the developing world, leading to decreased quality of life and poor economic consequences.[4] Furthermore, worldwide, sustainable healthcare models, regardless of payer type or insurance status, have not been identified for the ethical treatment of persons with chronic pain.[5] A cultural transformation in the way that we treat people with chronic pain should include them having equal access to pain management without consideration of public *vs* private provision of healthcare. Patients should have access to the most current evidence-based care by experienced pain clinicians, if required, rather than having treatment directed by managed care companies, public policies, and policy makers, and without judgement from the media, co-workers, family, and friends.

A central value of medicine is to ameliorate suffering in patients through the principles of non-maleficence, beneficence, justice, and respect for patient autonomy.[6] Most patients with chronic pain believe that they have the inalienable right to have their suffering adequately controlled through relief of their pains.[7] Even though some authors have argued that pains can be alleviated using modalities that are readily available,[8] most pain clinicians recognise that chronic pain is challenging to treat even under the best of circumstances. As pain clinicians we have a moral duty to speak frankly about ethical dilemmas, so as not to contribute to patient suffering or public health problems. Mindful awareness of the shared ethical practices of caring for persons with chronic pain should inform our core ethical values as healthcare providers.

Database searches (PubMed, PsychINFO, EMBASE, and SCOPUS) using the terms 'chronic pain and ethics', 'ethical decision-making and chronic pain', 'shared decision-making and chronic pain', and 'bioethics and chronic pain' identified only two recent books on ethical dilemmas exclusively faced in pain management. These were *Ethical Issues in Chronic Pain Management* by Michael E. Schatman[9] and *The Bioethics of Pain Management: Beyond Opioids* by Daniel S. Goldberg.[8] This limited literature on pain bioethics reflects the complexity of treating persons with chronic pain and offers little guidance to individual healthcare providers or members of interprofessional teams. A robust conversation is needed, about pain ethics in general and, more specifically, use of pain-related shared decision-making (SDM). Kaldjian's framework[10–12] for SDM is recommended because it incorporates the ethical principle of respect for patient autonomy within patient-centred care.

Pain, suffering, and ethics

Each person's pain is very real and deeply personal.[13] Pain is fundamental to life, a life without pain is not conducive to human flourishing.[2] Patients often struggle with the overwhelming nature of pain impacting most valued life domains, including work, family, spirituality, and recreation. Chronic pain leads to a decline in quality of life resulting in dysfunction that may be described as human suffering. Pain symptoms are frequently associated with suffering, but suffering is not confined to the experience of pain. No direct correlation has been identified with the amount of pain and the amount of suffering.